CO-ADMINISTRATION OF INTERLEUKIN-3 MUTANT POLYPEPTIDES WITH CSF'S FOR MULTI-LINEAGE HEMATOPOIETIC CELL PRODUCTION

Field of the Invention

The present invention relates to the coadministration or sequential treatment using mutants or variants of human interleukin-3 (hIL-3) and other colony stimulating factors (CSFs), cytokines, lymphokines, interleukins, hematopoietic growth factors or IL-3 variants.

Background of the Invention

Colony stimulating factors (CSFs) which stimulate the differentiation and/or proliferation of bone marrow cells have generated much interest because of their therapeutic potential for restoring depressed levels of hematopoietic stem cell-derived cells. CSFs in both human and murine systems have been identified and distinguished according to their activities. For example, granulocyte-CSF (G-CSF) and macrophage-CSF (M-CSF) stimulate the in vitro formation of neutrophilic granulocyte and macrophage colonies, respectively while GM-CSF and interleukin-3 (IL-3) have broader activities and stimulate the formation of both macrophage, neutrophilic and eosinophilic granulocyte colonies. IL-3 also stimulates the formation of mast, megakaryocyte and pure and mixed erythroid colonies (when erythropoietin is added).

Because of its ability to stimulate the proliferation of a number of different cell types and to support the growth and proliferation of progenitor cells, IL-3 has potential for therapeutic use in restoring hematopoietic cells to normal amounts in those cases where the number of cells has been reduced due to diseases or to therapeutic treatments such as radiation and/or chemotherapy.

Interleukin-3 (IL-3) is a hematopoietic growth factor which has the property of being able to promote the survival, growth and differentiation of hematopoietic cells. Among the biological properties of IL-3 are the ability (a) to support the growth and differentiation of progenitor cells committed to all, or virtually all, blood cell lineages; (b) to interact with early multipotential stem cells; (c) to sustain the growth of pluripotent precursor cells; (d) to stimulate proliferation of chronic myelogenous leukemia (CML) cells; (e) to stimulate proliferation of mast cells, eosinophils and basophils; (f) to stimulate DNA synthesis by human acute myelogenous leukemia (AML) cells; (g) to prime cells for production of leukotrienes and histamines; (h) to induce leukocyte chemotaxis; and (i) to induce cell surface molecules needed for leukocyte adhesion.

Mature human interleukin-3 (hIL-3) consists of 133 amino acids. It has one disulfide bridge and two potential glycosylation sites (Yang, et al., CELL 47:3 (1986)).

Murine IL-3 (mIL-3) was first identified by Ihle, et al., J. IMMUNOL. 126:2184 (1981) as a factor which induced expression of a T cell associated enzyme, 20`-hydroxysteroid dehydrogenase. The factor was purified to homogeneity and shown to regulate the growth and differentiation of numerous subclasses of early hematopoietic and lymphoid progenitor cells.

In 1984, cDNA clones coding for murine IL-3 were isolated (Fung, et al., NATURE 307:233 (1984) and Yokota, et al., PROC. NATL. ACAD. SCI. USA 81:1070 (1984)). The murine DNA sequence coded for a polypeptide of 166 amino acids including a putative signal peptide.

The gibbon IL-3 sequence was obtained using a gibbon cDNA expression library. The gibbon IL-3

sequence was then used as a probe against a human genomic library to obtain a human IL-3 sequence.

Gibbon and human genomic DNA homologues of the murine IL-3 sequence were disclosed by Yang, et al., CELL 47:3 (1986). The human sequence reported by Yang, et al. included a serine residue at position 8 of the mature protein sequence. Following this finding, others reported isolation of Pro^8 hIL-3 cDNAs having proline at position 8 of the protein sequence. Thus it appears that there may be two allelic forms of hIL-3.

Dorssers, et al., GENE 55:115 (1987), found a clone from a human cDNA library which hybridized with mIL-3. This hybridization was the result of the high degree of homology between the 3' noncoding regions of mIL-3 and hIL-3. This cDNA coded for an hIL-3 (Pro^8) sequence.

U.S. 4,877,729 and U.S. 4,959,454 disclose human IL-3 and gibbon IL-3 cDNAs and the protein sequences for which they code. The hIL-3 disclosed has serine rather than proline at position 8 in the protein sequence.

Clark-Lewis, et al., SCIENCE 231:134 (1986) performed a functional analysis of murine IL-3 analogs synthesized with an automated peptide synthesizer. The authors concluded that the stable tertiary structure of the complete molecule was required for full activity. A study on the role of the disulfide bridges showed that replacement of all four cysteines by alanine gave a molecule with 1/500th the activity as the native molecule. Replacement of two of the four Cys residues by Ala(Cys^{79}, Cys^{140} -> Ala^{79}, Ala^{140}) resulted in an increased activity. The authors concluded that in murine IL-3 a single disulfide bridge is required between cysteines 17 and 80 to get biological activity that approximates physiological levels and that this structure probably stabilizes the tertiary structure of the protein to give a conformation that is optimal for

function. (Clark-Lewis, et al., PROC. NATL. ACAD. SCI. USA 85:7897 (1988)).

International Patent Application (PCT) WO 88/00598 discloses gibbon- and human-like IL-3. The hIL-3 contains a Ser^8 -> Pro^8 replacement. Suggestions are made to replace Cys by Ser, thereby breaking the disulfide bridge, and to replace one or more amino acids at the glycosylation sites.

EP-A-0275598 (WO 88/04691) illustrates that Ala^1 can be deleted while retaining biological activity. Some mutant hIL-3 sequences are provided, e.g., two double mutants, Ala^1 -> Asp^1, Trp^{13} -> Arg^{13} (pGB/IL-302) and Ala^1 -> Asp^1, Met^3 -> Thr^3 (pGB/IL-304) and one triple mutant Ala^1 -> Asp^1, Leu^9 -> Pro^9, Trp^{13} -> Arg^{13} (pGB/IL-303).

WO 88/05469 describes how deglycosylation mutants can be obtained and suggests mutants of $Arg^{54}Arg^{55}$ and $Arg^{108}Arg^{109}Lys^{110}$ might avoid proteolysis upon expression in Saccharomyces cerevisiae by KEX2 protease. No mutated proteins are disclosed. Glycosylation and the KEX2 protease activity are only important, in this context, upon expression in yeast.

WO 88/06161 mentions various mutants which theoretically may be conformationally and antigenically neutral. The only actually performed mutations are Met^2 -> Ile^2 and Ile^{131} -> Leu^{131}. It is not disclosed whether the contemplated neutralities were obtained for these two mutations.

WO 91/00350 discloses nonglycosylated hIL-3 analog proteins, for example, hIL-3 ($Pro^8Asp^{15}Asp^{70}$), Met^3 rhuIL-3 ($Pro^8Asp^{15}Asp^{70}$); Thr^4 rhuIL-3 ($Pro^8Asp^{15}Asp^{70}$)and Thr^6 rhuIL-3 ($Pro^8Asp^{15}Asp^{70}$). It is said that these protein compositions do not exhibit certain adverse side effects associated with native hIL-3 such as urticaria resulting from infiltration of mast cells and lymphocytes into the dermis. The disclosed analog hIL-3 proteins may have N termini at

Met^3, Thr^4, or Thr^6.

WO 91/12874 discloses cysteine added variants (CAVs) of IL-3 which have at least one Cys residue substituted for a naturally occurring amino acid residue.

U.S. 4,810,643 discloses the DNA sequence encoding human G-CSF.

WO 91/07988 discloses a method to increase megakaryocyte production comprised of administration of G-CSF with IL-3 or GM-CSF. Also disclosed is a method for increasing platelet production comprised of administration of IL-6 with IL-3, G-CSF or GM-CSF.

Summary of the Invention

The present invention encompasses recombinant human interleukin-3 (hIL-3) variant or mutant proteins (muteins) These hIL-3 muteins contain amino acid substitutions and may also have amino acid deletions at either/or both the N- and C- termini. This invention encompasses coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors (CSFs), cytokines, lymphokines, interleukins, hematopoietic growth factors (herein after collectively referred to as "colony stimulating factors") which may have the potential for therapeutic use in restoring hematopoietic cells to normal amounts in those cases where the number of cells has been reduced due to diseases or to therapeutic treatments such as radiation and/or chemotherapy. Coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors may enhance therapeutic value due to the synergistic effects of the proteins that make up the treatment. The use of multiple factors may also have the potential advantage by lowering the demands

placed on factor-producing cells and their induction systems. If there are limitations in the ability of a cell to produce a factor then by lowering the required concentrations of each of the factors by using them in combination may usefully reduce demands on the factor-producing cells. The use of multiple factors may lower the amount of the factors that would be needed, probably reducing the likelihood of adverse responses.

Coadministration or sequential treatment may have the usual activity of the peptides forming the mixture or it may be further characterized by having a biological or physiological activity greater than simply the additive function of the presence of IL-3 or the other growth factors alone. Coadministration or sequential treatment may also unexpectedly provide an enhanced effect on the activity or an activity different from that expected by the presence of IL-3 or the other growth factors. The IL-3 variants of the present invention may also have an improved activity profile which may include reduction of undesirable biological activities associated with native hIL-3.

The present invention includes mutants of hIL-3 in which from 1 to 14 amino acids have been deleted from the N-terminus and/or from 1 to 15 amino acids have been deleted from the C-terminus, containing multiple amino acid substitutions, which are used with other growth factors or IL-3 variant. Preferred IL-3 variants of the present invention include variants in which amino acids 1 to 14 have been deleted from the N-terminus, amino acids 126 to 133 have been deleted from the C-terminus and contain from about four to about twenty-six amino acid substitutions in the polypeptide sequence.

The present invention also provides IL-3 variants

which may function as IL-3 antagonists or as discrete antigenic fragments for the production of antibodies useful in immunoassay and immunotherapy protocols. Antagonists of hIL-3 would be particularly useful in blocking the growth of certain cancer cells like AML, CML and certain types of B lymphoid cancers. Other conditions where antagonists would be useful include those in which certain blood cells are produced at abnormally high numbers or are being activated by endogenous ligands. Antagonists would effectively compete for ligands, presumably naturally occurring hemopoietins including and not limited to IL-3, GM-CSF and IL-5, which might trigger or augment the growth of cancer cells by virtue of their ability to bind to the IL-3 receptor complex while intrinsic activation properties of the ligand are diminished. IL-3, GM-CSF and/or IL-5 also play a role in certain asthmatic responses. An antagonist of the IL-3 receptor may have the utility in this disease by blocking receptor-mediated activation and recruitment of inflammatory cells.

In addition to the use of the IL-3 variants of the present invention with other colony stimulating factors in vivo, it is envisioned that in vitro uses would include the ability to stimulate bone marrow and blood cell activation and growth before infusion into patients.

Brief Description of the Drawings

Figure 1 is the human IL-3 gene for E.coli expression (pMON5873), encoding the polypeptide sequence of natural (wild type) human IL-3 [SEQ ID NO:128], plus an initiator methionine, as expressed in E. coli, with the amino acids numbered from the N-terminus of the natural hIL-3.

Figure 2 shows the synergistic effects, in the methylcellulose assay, of the IL-3 variant, pMON13288, with G-CSF compared to the synergy of native IL-3 with G-CSF . Also shown are the effects of native IL-3 and the IL-3 variant, pMON13288, alone. The concentration of IL-3 is plotted versus the colony counts per 100,000 starting CD34+ cells.

Figure 3 shows the synergistic effects, in the methylcellulose assay, of the IL-3 variant, pMON13288, with GM-CSF compared to the synergy of native IL-3 with GM-CSF . Also shown are the effects of native IL-3 and the IL-3 variant, pMON13288, alone. The concentration of IL-3 is plotted versus the colony counts per 100,000 starting CD34+ cells.

Figure 4 shows the synergistic effects, in the cord blood assay, of the IL-3 variant, pMON13288, with stem cell factor (SCF) compared to the synergy of native IL-3 (pMON5873) with stem cell factor (SCF). Also shown are the effects of native IL-3 (pMON5873) and the IL-3 variant, pMON13288, alone. The concentration of IL-3 is plotted versus the colony counts (CFU) per 10,000 starting CD34+ cells.

Figure 5 shows the synergistic effects, in the cord blood assay, of the IL-3 variant, pMON13288, with stem cell factor (SCF) compared to the synergy of native IL-3 (PMON5873) with stem cell factor (SCF). Also shown are the effects of native IL-3 (PMON5873) and the IL-3 variant, pMON13288, alone. The concentration of IL-3 is plotted versus the colony counts (CFU) per 10,000 starting CD34+ cells.

Detailed Description of the Invention

The present invention encompasses the coadministration or sequential treatment with recombinant human interleukin-3 (hIL-3) variant or mutant proteins (muteins) with other colony stimulating factors (CSFs), cytokines, lymphokines, interleukins, hematopoietic growth factors and variants thereof (herein after collectively referred to as "colony stimulating factors"). This invention encompasses the coadministration or sequential treatment using IL-3 variants and other colony stimulating factors colony stimulating factors, each of which may act through a different and specific cell receptor to initiate complementary biological activities. Hematopoiesis requires a complex series of cellular events in which stem cells generate continuously into large populations of maturing cells in all major lineages. There are currently at least 20 known regulators with hematopoietic proliferative activity. Most of these proliferative regulators can stimulate one or another type of colony formation in vitro, the precise pattern of colony formation stimulated by each regulator is quite distinctive. No two regulators stimulate exactly the same pattern of colony formation, as evaluated by colony numbers or, more importantly, by the lineage and maturation pattern of the cells making up the developing colonies. Proliferative responses can most readily be analyzed in simplified in vitro culture systems. Three quite different parameters can be distinguished: alteration in colony size, alteration in colony numbers and cell lineage. Two or more factors may act on the progenitor cell, inducing the formation of larger number of progeny thereby increasing the colony size. Two or more factors may allow increased number of progenitor cells to proliferate either because distinct subsets of progenitors cells exist that respond exclusively to one factor or because some progenitors require stimulation by two or more factors

before being able to respond. Activation of additional receptors on a cell by the use of two or more factors is likely to enhance the mitotic signal because of coalescence of initially differing signal pathways into a common final pathway reaching the nucleus (Metcalf, 1989). Other mechanism could explain synergy. For example, if one signaling pathway is limited by an intermediate activation of an additional signaling pathway by a second factor may result in a superadditive response. In some cases, activation of one receptor type can induce an enhanced expression of other receptors (Metcalf, 1993). Two or more factors may result in a different pattern of cell lineages then from a single factor. The use of the IL-3 variants of the present invention with other colony stimulating factors may have the potential clinical advantage resulting from a proliferative response that is not possible by any single factor.

Hematopoietic and other growth factors can be grouped in to two distinct families of related receptors: (1) tyrosine kinase receptors, including those for epidermal growth factor, M-CSF (Sherr, 1990) and SCF (Yarden et al., 1987): and (2) hematopoietic receptors, not containing a tyrosine kinase domain, but exhibiting obvious homology in their extracellular domain (Bazan, 1990). Included in the later group are erythropoietin (D'Andrea et al., 1989), GM-CSF (Gearing et al., 1989), IL-3 (Kitamura et al., 1991), G-CSF (Fukunaga et al., 1990), IL-4 (Harada et al., 1990), IL-5 (Takaki et al., 1990), IL-6 (Yamasaki et al., 1988), IL-7 (Goodwin et al., 1990), LIF (Gearing et al., 1991) and IL-2 (Cosman et al., 1987). Most of the later group of receptors exists in high-affinity form as a heterodimers. After ligand binding, the specific α-chains become associated with at least one other receptor chain (β-chain, γ-chain). Many of these factors share a common receptor

subunit. The α-chains for GM-CSF, IL-3 and IL-5 share the same β-chain (Kitamura et al., 1991) and receptor complexes for IL-6, LIF and IL-11 share a common β-chain (gp130) (Taga et al., 1989; Gearing et al., 1992). The receptor complexes of IL-2, IL-4 and IL-7 share a common γ-chain (Kondo et al., 1993; Russell et al., 1993; Noguchi et al., 1993).

GM-CSF accelerates recovery of neutrophils and maintains functional capacity, yet has little demonstrable effect on platelet recovery. In contrast IL-3 promotes a slower increase recovery in neutrophils and monocytes while accelerating the recovery of platelets.

Recent studies in normal primates indicate that when IL-3 was administered before GM-CSF that the combination of IL-3 and GM-CSF promoted a synergistic rise in peripheral white blood cells and platelets (Donahue R. E. et al., 1988; Krumwieh D. et al., 1988; and Stahl C.P. et al., 1992). The synergistic effect observed in the sequential combination of IL-3 before GM-CSF may result from the expansion of GM-CSF sensitive cells by IL-3 resulting in a more efficient production of neutrophils. The coadministration of GM-CSF and IL-3 resulted in diminished neutrophils production relative to GM-CSF alone (Farese et al., 1993). The coadministration of IL-3 and GM-CSF, may result in down regulation of GM-CSF receptors by IL-3 thereby dampening the GM-CSF induced increase in neutrophils. However the coadministration of IL-3 and GM-CSF in a marrow-ablated rhesus monkeys promoted accelerated platelets and neutrophil recovery relative to sequential cytokine treatment or with either IL-3 or GM-CSF alone (Farese et al., 1993).

The in vitro activity of both IL-3 and GM-CSF has

been shown to be additive with respect to stimulating larger colonies than either cytokine alone (Robinson et al., 1987; Bruno et al., 1989; Metcalf et al., 1992; Bruno et al., 1991; Bridell et al., 1990). Recently IL-12 has been shown to synergize with IL-3 and c-kit (stem cell factor) to enhance the recovery of hemopoietic stem cells in liquid culture (Ploemacher et al., 1993).

Recent in vitro (Emerson et al., 1988: Sonodo et al., 1988) and in vivo (Ganser et al., 1992; Donahue R. E. et al., 1988; Krumwieh D. et al., 1988; and Stahl C.P. et al., 1992) results of combined IL-3 and GM-CSF treatment suggests an increased clinical efficacy in cytokine combination treatment.

As mentioned earlier some of the factors that are involved in hematopoiesis are limited to a specific cell lineage and others have much broader effects and may result in the proliferation and support of multi-lineages and there may be considerable overlap between these factors but that the proliferative profiles are distinct. This suggests that the coadministration or sequential treatment with multiple factors may have a clinical advantage. IL-3 variants of the present invention that have an increased therapeutic index, compared to native IL-3, may have a distinct clinical advantage when coadministered or used sequentially in treatment.

The use of multiple factors may also have potential advantage by lowering the demands placed on factor-producing cells and their induction systems. If there are limitations in the ability of a cell to produce a factor then by lowering the required concentrations of each of the factors by using them in combination may usefully reduce demands on the factor-producing cells. The use of multiple factors may lower

the amount of the factors that would be needed, probably reducing the likelihood of adverse responses.

A non-exclusive list of growth factors, colony stimulating factors (CSFs) including; cytokines, lymphokines, interleukins, hematopoietic growth factors, which can be used in coadministration or sequential treatment with the hIL-3 variant of the present invention include GM-CSF, CSF-1, G-CSF, Meg-CSF (more recently referred to as c-mpl ligand), M-CSF, erythropoietin (EPO), IL-1, IL-4, IL-2, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, LIF, flt3/flk2, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor (SCF) also known as steel factor or c-kit ligand and variants thereof.

The present invention relates to novel variants of human interleukin-3 (hIL-3) in which amino acid substitutions have been made at four or more positions in amino acid sequence of the polypeptide used in sequential treatment or coadministration with other colony stimulating factors. Preferred IL-3 variants of the present invention which have deletions of amino acids 1 to 14 at the N-terminus and 126 to 133 at the C-terminus and which also have four or more amino acid substitutions in the polypeptide used in coadministered or sequential treatment with other colony stimulating factors or IL-3 variants. Among the preferred IL-3 variants are those having twenty-six amino acid substitutions. The present invention includes mutant polypeptides comprising minimally amino acids 15 to 118 of hIL-3 with or without additional amino acid extensions to the N-terminus and/or C-terminus which further contain four or more amino acid substitutions in the amino acid sequence of the polypeptide.

As used herein human interleukin-3 corresponds to the amino acid sequence (1-133) as depicted in Figure 1 and (15-125) hIL-3 corresponds to the 15 to 125 amino acid sequence of the hIL-3 polypeptide. Naturally occurring variants of hIL-3 polypeptide amino acids are also included in the present invention (for example, the allele in which proline rather than serine is at position 8 in the hIL-3 polypeptide sequence) as are variant hIL-3 molecules which are modified post-translationally (e.g. glycosylation).

"Mutant amino acid sequence," "mutant protein" or "mutant polypeptide" refers to a polypeptide having an amino acid sequence which varies from a native sequence or is encoded by a nucleotide sequence intentionally made variant from a native sequence. "Mutant protein," "variant protein" or "mutein" means a protein comprising a mutant amino acid sequence and includes polypeptides which differ from the amino acid sequence of native hIL-3 due to amino acid deletions, substitutions, or both. "Native sequence" refers to an amino acid or nucleic acid sequence which is identical to a wild-type or native form of a gene or protein.

Human IL-3 can be characterized by its ability to stimulate colony formation by human hematopoietic progenitor cells. The colonies formed include erythroid, granulocyte, megakaryocyte, granulocytic macrophages and mixtures thereof. Human IL-3 has demonstrated an ability to restore bone marrow function and peripheral blood cell populations to therapeutically beneficial levels in studies performed initially in primates and subsequently in humans (Gillio, A. P., et al. (1990); Ganser, A, et al. (1990); Falk, S., et al. (1991). Additional activities of hIL-3 include the ability to stimulate leukocyte

migration and chemotaxis; the ability to prime human leukocytes to produce high levels of inflammatory mediators like leukotrienes and histamine; the ability to induce cell surface expression of molecules needed for leukocyte adhesion; and the ability to trigger dermal inflammatory responses and fever. Many or all of these biological activities of hIL-3 involve signal transduction and high affinity receptor binding. Coadministration or sequential treatment using the IL-3 variants of the present invention with other colony stimulating factors may exhibit useful properties such as having similar or greater biological activity when compared to native hIL-3 or by having improved half-life or decreased adverse side effects, or a combination of these properties. The IL-3 variants of the present invention may also be useful as antagonists. IL-3 variants which have little or no activity when compared to native hIL-3 may still be useful as antagonists, as antigens for the production of antibodies for use in immunology or immunotherapy, as genetic probes or as intermediates used to construct other useful hIL-3 muteins.

The use of IL-3 variants of the present invention when coadministered or as part of sequential treatment will preferably have at least one biological property of human IL-3. Coadministration or sequential treatment may also have more than one IL-3-like biological property, or an improved property, or a reduction in an undesirable biological property of human IL-3. Some mutant polypeptides of the present invention may also exhibit an improved side effect profile. For example, they may exhibit a decrease in leukotriene release or histamine release when compared to native hIL-3 or (15-125) hIL-3. Such hIL-3 or hIL-3-like biological properties may include one or more of the following biological characteristics and in vivo and in vitro activities.

One such property is the support of the growth and differentiation of progenitor cells committed to erythroid, lymphoid, and myeloid lineages. For example, in a standard human bone marrow assay, an IL-3-like biological property is the stimulation of granulocytic type colonies, megakaryocytic type colonies, monocyte/macrophage type colonies, and erythroid bursts. Other IL-3-like properties are the interaction with early multipotential stem cells, the sustaining of the growth of pluripotent precursor cells, the ability to stimulate chronic myelogenous leukemia (CML) cell proliferation, the stimulation of proliferation of mast cells, the ability to support the growth of various factor-dependent cell lines, and the ability to trigger immature bone marrow cell progenitors. Other biological properties of IL-3 have been disclosed in the art. Human IL-3 also has some biological activities which may in some cases be undesirable, for example the ability to stimulate leukotriene release and the ability to stimulate increased histamine synthesis in spleen and bone marrow cultures and in vivo.

Biological activity of hIL-3 and hIL-3 variant proteins of the present invention is determined by DNA synthesis by human acute myelogenous leukemia cells (AML). The factor-dependent cell line AML 193 was adapted for use in testing biological activity. The biological activity of hIL-3 and hIL-3 variant proteins of the present invention is also determined by counting the colony forming units in a bone marrow assay.

Other in vitro cell based assays may also be useful to determine the synergistic effect of multiple colony stimulating factors that comprise the mixture. The following are examples of other useful assays.

TF-1 proliferation assay: The TF-1 cell line was

derived from bone marrow of a patient with erythroleukemia (Kitamura et al., 1989). TF-1 cells respond to IL-3, GM-CSF, EPO and IL-5.
32D proliferation assay: 32D is a murine IL-3 dependent cell line which does not respond to human IL-3 but does respond to human G-CSF which is not species restricted.
T1165 proliferation assay: T1165 cells are a IL-6 dependent murine cell line (Nordan et al., 1986) which respond to IL-6 and IL-11.
Human Plasma Clot meg-CSF Assay: Used to assay megakaryocyte colony formation activity (Mazur et al., 1981).

One object of the present invention is to provide hIL-3 variant with four or more amino acid substitutions in the polypeptide sequence used in coadministration or sequential treatment with other colony stimulating factors or IL-3 variants, which have similar or improved biological activity in relation to native hIL-3 or the other colony stimulating factors or IL-3 variant.

The hIL-3 variants of the present invention may have hIL-3 or hIL-3-like activity. For example, they may possess one or more of the biological activities of native hIL-3 and may be useful in stimulating the production of hematopoietic cells by human or primate progenitor cells. The IL-3 variants of the present invention and pharmaceutical compositions containing them may be useful in the treatment of conditions in which hematopoietic cell populations have been reduced or destroyed due to disease or to treatments such as radiation or chemotherapy. Pharmaceutical compositions containing IL-3 variants of the present invention can be administered parenterally, intravenously, or subcutaneously.

Native hIL-3 possesses considerable inflammatory activity and has been shown to stimulate synthesis of the arachidonic acid metabolites LTC_4, LTD_4, and LTE_4; histamine synthesis and histamine release. Human clinical trials with native hIL-3 have documented inflammatory responses (Biesma, et al., BLOOD, 80:1141-1148 (1992) and Postmus, et al., J. CLIN. ONCOL., 10:1131-1140 (1992)). A recent study indicates that leukotrienes were involved in IL-3 actions in vivo and may contribute significantly to the biological effects of IL-3 treatment (Denzlinger, C., et al., BLOOD, 81:2466-2470 (1993))

Some IL-3 variants of the present invention, when co-administered with other CSFs, cytokines, lymphokines, interleukins, hematopoietic growth factors or IL-3 variants, may have an improved therapeutic profile as compared to native hIL-3 or (15-125)hIL-3. For example, some IL-3 variants of the present invention may have a similar or more potent growth factor activity relative to native hIL-3 or (15-125)hIL-3 without having a similar or corresponding increase in the stimulation of leukotriene or histamine. These IL-3 variants would be expected to have a more favorable therapeutic profile since the amount of polypeptide which needs to be given to achieve the desired growth factor activity (e.g. cell proliferation) would have a diminished leukotriene or histamine stimulating effect. In studies with native hIL-3, the stimulation of inflammatory factors has been an undesirable side effect of the treatment. Reduction or elimination of the stimulation of mediators of inflammation would provide an advantage over the use of native hIL-3.

Novel IL-3 variants of the present invention may also be useful as antagonists which block the hIL-3 receptor by binding specifically to it and preventing binding of the agonist.

One potential advantage of the novel IL-3 variants of the present invention, particularly those which retain activity similar to or better than that of native hIL-3, is that it may be possible to use a smaller amount of the biologically active mutein to produce the desired therapeutic effect. This may make it possible to reduce the number of treatments necessary to produce the desired therapeutic effect. The use of smaller amounts may also reduce the possibility of any potential antigenic effects or other possible undesirable side effects. For example, if a desired therapeutic effect can be achieved with a smaller amount of polypeptide it may be possible to reduce or eliminate side effects associated with the administration of native IL-3 such as the stimulation of leukotriene and/or histamine release. The novel IL-3 variants of the present invention may also be useful in the activation of stem cells or progenitors which have low receptor numbers.

Compounds of this invention are preferably made by genetic engineering techniques now standard in the art United States Patent 4,935,233 and Sambrook et al., "Molecular Cloning. A Laboratory Manual", Cold Spring Harbor Laboratory (1989)]. One method of creating the preferred hIL-3 (15-125) mutant genes is cassette mutagenesis [Wells, et al. (1985)] in which a portion of the coding sequence of hIL-3 in a plasmid is replaced with synthetic oligonucleotides that encode the desired amino acid substitutions in a portion of the gene between two restriction sites. In a similar manner amino acid substitutions could be made in the full-length hIL-3 gene, or genes encoding variants of hIL-3 in which from 1 to 14 amino acids have been deleted from the N-terminus and/or from 1 to 15 amino acids have been deleted from the C-terminus. When properly assembled these oligonucleotides would encode

hIL-3 variants with the desired amino acid substitutions and/or deletions from the N-terminus and/or C-terminus. These and other mutations could be created by those skilled in the art by other mutagenesis methods including; oligonucleotide-directed mutagenesis [Zoller and Smith (1982, 1983, 1984), Smith (1985), Kunkel (1985), Taylor, et al. (1985), Deng and Nickoloff (1992)] or polymerase chain reaction (PCR) techniques [Saiki, (1985)].

Plasmid DNA can be treated with the chosen restriction endonucleases then ligated to the annealed oligonucleotides. The ligated mixtures can be used to transform competent JM101 cells to resistance to an appropriate antibiotic. Single colonies can be picked and the plasmid DNA examined by restriction analysis and/or DNA sequencing to identify plasmids with mutant hIL-3 genes.

Suitable cells or cell lines for the production of the proteins claimed in the present invention may be bacterial cells. For example, the various strains of E. coli are well-known as host cells in the field of biotechnology. Examples of such strains include E. coli strains JM101 [Yanish-Perron, et al. (1985)] and MON105 [Obukowicz, et al. (1992)]. Also included in the present invention is the expression of the IL-3 variant protein utilizing a chromosomal expression vector for E. coli based on the bacteriophage Mu (Weinberg et al., 1993). Various strains of B. subtilis may also be employed as host cells for expression of the polypeptides of the present invention. Many strains of yeast cells known to those skilled in the art are also available as host cells for expression of the polypeptides of the present invention. When expressed in the E. coli cytoplasm, the above-mentioned mutant hIL-3 variants of the

present invention may also be constructed with Met-Ala- at the N-terminus so that upon expression the Met is cleaved off leaving Ala at the N-terminus. The IL-3 variant proteins of the present invention may include polypeptides having Met-, Ala- or Met-Ala- attached to the N-terminus. When the IL-3 variant polypeptides are expressed in the cytoplasm of E. coli, polypeptides with and without Met attached to the N-terminus are obtained. The N-termini of proteins made in the cytoplasm of E. coli are affected by posttranslational processing by methionine aminopeptidase (Ben-Bassat et al., 1987) and possibly by other peptidases. These IL-3 variant proteins may also be expressed in E. coli by fusing a signal peptide to the N-terminus. This signal peptide is cleaved from the polypeptide as part of the secretion process. Secretion in E. coli can be used to obtain the correct amino acid at the N-terminus (e.g., Asn^{15} in the (15-125) hIL-3 polypeptide) due to the precise nature of the signal peptidase. This is in contrast to the heterogeneity which may be observed at the N-terminus of proteins expressed in the cytoplasm in E. coli.

Also suitable for use in the present invention are mammalian cells, such as Chinese hamster ovary cells (CHO). General methods for expression of foreign genes in mammalian cells are reviewed in: Kaufman, R. J. (1987) High level production of proteins in mammalian cells, in Genetic Engineering, Principles and Methods, Vol. 9, J. K. Setlow, editor, Plenum Press, New York. An expression vector is constructed in which a strong promoter capable of functioning in mammalian cells drives transcription of a eukaryotic secretion signal peptide coding region, which is translationally fused to the coding region for the IL-3 variant. For example, plasmids such as pcDNA I/Neo, pRc/RSV, and pRc/CMV (obtained from Invitrogen Corp., San Diego,

California) can be used. The eukaryotic secretion signal peptide coding region can be from the hIL-3 gene itself or it can be from another secreted mammalian protein (Bayne, M. L. et al. (1987) Proc. Natl. Acad. Sci. USA 84, 2638-2642). After construction of the vector containing the hIL-3 variant gene, the vector DNA is transfected into mammalian cells. Such cells can be, for example, the COS7, HeLa, BHK, CHO, or mouse L lines. The cells can be cultured, for example, in DMEM media (JRH Scientific). The hIL-3 variant secreted into the media can be recovered by standard biochemical approaches following transient expression 24 - 72 hours after transfection of the cells or after establishment of stable cell lines following selection for neomycin resistance. The selection of suitable mammalian host cells and methods for transformation, culture, amplification, screening and product production and purification are known in the art. See, e.g., Gething and Sambrook, Nature, 293:620-625 (1981), or alternatively, Kaufman et al, Mol. Cell. Biol., 5(7):1750-1759 (1985) or Howley et al., U.S. Pat. No. 4,419,446. Another suitable mammalian cell line is the monkey COS-1 cell line. A similarly useful mammalian cell line is the CV-1 cell line.

Where desired, insect cells may be utilized as host cells in the method of the present invention. See, e.g. Miller et al, Genetic Engineering, 8:277-298 (Plenum Press 1986) and references cited therein. In addition, general methods for expression of foreign genes in insect cells using Baculovirus vectors are described in: Summers, M. D. and Smith, G. E. (1987) - A manual of methods for Baculovirus vectors and insect cell culture procedures, Texas Agricultural Experiment Station Bulletin No. 1555. An expression vector is constructed comprising a Baculovirus transfer vector, in which a strong Baculovirus promoter (such as the polyhedron promoter) drives transcription of a

eukaryotic secretion signal peptide coding region, which is translationally fused to the coding region for the IL-3 variant polypeptide. For example, the plasmid pVL1392 (obtained from Invitrogen Corp., San Diego, California) can be used. After construction of the vector carrying the gene encoding the IL-3 variant polypeptide, two micrograms of this DNA is cotransfected with one microgram of Baculovirus DNA (see Summers & Smith, 1987) into insect cells, strain SF9. Pure recombinant Baculovirus carrying the IL-3 variant gene is used to infect cells cultured, for example, in Excell 401 serum-free medium (JRH Biosciences, Lenexa, Kansas). The IL-3 variant protein secreted into the medium can be recovered by standard biochemical approaches. Supernatants from mammalian or insect cells expressing the IL-3 variant protein can be first concentrated using any of an number of commercial concentration units.

Coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors may be useful in the treatment of diseases characterized by a decreased levels of either myeloid, erythroid, lymphoid, or megakaryocyte cells of the hematopoietic system or combinations thereof. In addition, they may be used to activate mature myeloid and/or lymphoid cells. Among conditions susceptible to treatment with the polypeptides of the present invention is leukopenia, a reduction in the number of circulating leukocytes (white cells) in the peripheral blood. Leukopenia may be induced by exposure to certain viruses or to radiation. It is often a side effect of various forms of cancer therapy, e.g., exposure to chemotherapeutic drugs, radiation and of infection or hemorrhage. Therapeutic treatment of leukopenia with these IL-3 variants of the present invention with other colony stimulating factors may

avoid undesirable side effects caused by treatment with presently available drugs.

Coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors may be useful in the treatment of neutropenia and, for example, in the treatment of such conditions as aplastic anemia, cyclic neutropenia, idiopathic neutropenia, Chediak-Higashi syndrome, systemic lupus erythematosus (SLE), leukemia, myelodysplastic syndrome and myelofibrosis.

The IL-3 variants of the present invention, when coadministered or used in sequential treatment with other colony stimulating factors, may be useful in the treatment or prevention of thrombocytopenia. Currently the only therapy for thrombocytopenia is platelet transfusions which are costly and carry the significant risks of infection (HIV, HBV) and alloimunization. The IL-3 variants, when coadministered or used in sequential treatment with other colony stimulating factors, may alleviate or diminish the need for platelet transfusions. Severe thrombocytopenia may result from genetic defects such as Fanconi's Anemia, Wiscott-Aldrich, or May-Hegglin syndromes. Acquired thrombocytopenia may result from auto- or allo-antibodies as in Immune Thrombocytopenia Purpura, Systemic Lupus Erythromatosis, hemolytic anemia, or fetal maternal incompatibility. In addition, splenomegaly, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, infection or prosthetic heart valves may result in thrombocytopenia. Severe thrombocytopenia may also result from chemotherapy and/or radiation therapy or cancer. Thrombocytopenia may also result from marrow invasion by carcinoma, lymphoma, leukemia or fibrosis.

The IL-3 variants of the present invention, when coadministered or used in sequential treatment with other colony stimulating factors, may be useful in the mobilization of hematopoietic progenitors and stem cells into peripheral blood. Peripheral blood derived progenitors have been shown to be effective in reconstituting patients in the setting of autologous marrow transplantation. Hematopoietic growth factors including G-CSF and GM-CSF have been shown to enhance the number of circulating progenitors and stem cells in the peripheral blood. This has simplified the procedure for peripheral stem cell collection and dramatically decreased the cost of the procedure by decreasing the number of pheresis required. The IL-3 variants, when coadministered or used in sequential treatment with other colony stimulating factors, may be useful in mobilization of stem cells and further enhance the efficacy of peripheral stem cell transplantation.

Another projected clinical use of growth factors has been in the in vitro activation of hematopoietic progenitors and stem cells for gene therapy. In order to have the gene of interest incorporated into the genome of the hematopoietic progenitor or stem cell one needs to stimulate cell division and DNA replication. Hematopoietic stem cells cycle at a very low frequency which means that growth factors may be useful to promote gene transduction and thereby enhance the clinical prospects for gene therapy.

Many drugs may cause bone marrow suppression or hematopoietic deficiencies. Examples of such drugs are AZT, DDI, alkylating agents and anti-metabolites used in chemotherapy, antibiotics such as chloramphenicol, penicillin, gancyclovir, daunomycin and sulfa drugs,

phenothiazones, tranquilizers such as meprobamate, analgesics such as aminopyrine and dipyrone, anticonvulsants such as phenytoin or carbamazepine , antithyroids such as propylthiouracil and methimazole and diuretics. Coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors may be useful in preventing or treating the bone marrow suppression or hematopoietic deficiencies which often occur in patients treated with these drugs.

Hematopoietic deficiencies may also occur as a result of viral, microbial or parasitic infections and as a result of treatment for renal disease or renal failure, e.g., dialysis. Coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors may be useful in treating such hematopoietic deficiency.

The treatment of hematopoietic deficiency may include administration of a pharmaceutical composition containing the IL-3 variants with other colony stimulating factors to a patient. Coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors may also be useful for the activation and amplification of hematopoietic precursor cells by treating these cells in vitro with the coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors prior to injecting the cells into a patient.

Various immunodeficiencies e.g., in T and/or B lymphocytes, or immune disorders, e.g., rheumatoid arthritis, may also be beneficially affected by treatment with the coadministration or sequential treatment using IL-3 variants of the present invention with other colony stimulating factors molecules of the present invention. Immunodeficiencies may be the result of viral infections e.g. HTLVI, HTLVII, HTLVIII,

severe exposure to radiation, cancer therapy or the result of other medical treatment. IL-3 variants of the present invention may also be employed, alone or in combination with other hematopoietins, in the treatment of other blood cell deficiencies, including thrombocytopenia (platelet deficiency), or anemia. Other uses for these novel polypeptides are in the treatment of patients recovering from bone marrow transplants in vivo and ex vivo, and in the development of monoclonal and polyclonal antibodies generated by standard methods for diagnostic or therapeutic use.

Other aspects of the present invention are methods and therapeutic compositions for treating the conditions referred to above. Such compositions comprise a therapeutically effective amount of one or more of the IL-3 variants of the present invention with other colony stimulating factors in a mixture with a pharmaceutically acceptable carrier. This composition can be administered either parenterally, intravenously or subcutaneously. When administered, the therapeutic composition for use in this invention is preferably in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such a parenterally acceptable protein solution, having due regard to pH, isotonicity, stability and the like, is within the skill of the art.

The dosage regimen involved in a method for treating the above-described conditions will be determined by the attending physician considering various factors which modify the action of drugs, e.g. the condition, body weight, sex and diet of the patient, the severity of any infection, time of administration and other clinical factors. Generally, a daily regimen may be in the range of 0.2 - 150 μg/kg of IL-3 variant protein per kilogram of body weight. This dosage regimen is referenced to a standard level of biological activity which recognizes that native IL-

3 generally possesses an EC_{50} at or about 10 picoMolar to 100 picoMolar in the AML proliferation assay described herein. Therefore, dosages would be adjusted relative to the activity of a given IL-3 variant protein vs. the activity of native (reference) IL-3 and it would not be unreasonable to note that dosage regimens may include doses as low as 0.1 microgram and as high as 1 milligram per kilogram of body weight per day. In addition, there may exist specific circumstances where dosages of IL-3 variant protein would be adjusted higher or lower than the range of 10 - 200 micrograms per kilogram of body weight. These include co-administration with other CSF, cytokine, lymphokine, interleukin, hematopoietic growth factor or IL-3 variant or growth factors; co-administration with chemotherapeutic drugs and/or radiation; the use of glycosylated IL-3 proteins; and various patient-related issues mentioned earlier in this section. As indicated above, the therapeutic method and compositions may also include co-administration with other human factors. A non-exclusive list of other appropriate hematopoietins, CSFs, cytokines, lymphokines, hematopoietic growth factors and interleukins for simultaneous or serial co-administration with the polypeptides of the present invention includes GM-CSF, CSF-1, G-CSF, Meg-CSF (more recently referred to as c-mpl ligand), M-CSF, erythropoietin (EPO), IL-1, IL-4, IL-2, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, LIF, flt3/flk2, human growth hormone, B-cell growth factor, B-cell differentiation factor and eosinophil differentiation factor, stem cell factor (SCF) also known as steel factor or c-kit ligand, or combinations thereof. The dosage recited above would be adjusted to compensate for such additional components in the therapeutic composition. Progress of the treated patient can be monitored by periodic assessment of the hematological profile, e.g., differential cell count

and the like.

The present invention includes the following compositions:

1. A composition comprising:

A human interleukin-3 mutant polypeptide of the Formula:

```
Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn
 1               5                  10                  15

Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                20                  25                  30

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Xaa Xaa Xaa
                35                  40                  45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                50                  55                  60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                65                  70                  75

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                80                  85                  90

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                95                 100                 105

Xaa Phe Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
               110                 115                 120

Xaa Xaa Xaa Gln Gln Thr Thr Leu Ser Leu Ala Ile Phe
               125                 130
```

[SEQ ID NO:1]

wherein
Xaa at position 17 is Ser, Lys, Gly, Asp, Met, Gln, or Arg;
Xaa at position 18 is Asn, His, Leu, Ile, Phe, Arg, or Gln;
Xaa at position 19 is Met, Phe, Ile, Arg, Gly, Ala, or Cys;
Xaa at position 20 is Ile, Cys, Gln, Glu, Arg, Pro, or Ala;
Xaa at position 21 is Asp, Phe, Lys, Arg, Ala, Gly, Glu, Gln, Asn, Thr, Ser or Val;
Xaa at position 22 is Glu, Trp, Pro, Ser, Ala, His, Asp, Asn, Gln, Leu, Val or Gly;
Xaa at position 23 is Ile, Val, Ala, Leu, Gly, Trp, Lys, Phe, Leu, Ser, or Arg;
Xaa at position 24 is Ile, Gly, Val, Arg, Ser, Phe, or Leu;
Xaa at position 25 is Thr, His, Gly, Gln, Arg, Pro, or Ala;
Xaa at position 26 is His, Thr, Phe, Gly, Arg, Ala, or Trp;
Xaa at position 27 is Leu, Gly, Arg, Thr, Ser, or Ala;
Xaa at position 28 is Lys, Arg, Leu, Gln, Gly, Pro, Val or Trp;
Xaa at position 29 is Gln, Asn, Leu, Pro, Arg, or Val;
Xaa at position 30 is Pro, His, Thr, Gly, Asp, Gln, Ser, Leu, or Lys;
Xaa at position 31 is Pro, Asp, Gly, Ala, Arg, Leu, or Gln;
Xaa at position 32 is Leu, Val, Arg, Gln, Asn, Gly, Ala, or Glu;
Xaa at position 33 is Pro, Leu, Gln, Ala, Thr, or Glu;
Xaa at position 34 is Leu, Val, Gly, Ser, Lys, Glu, Gln, Thr, Arg, Ala, Phe, Ile or Met;
Xaa at position 35 is Leu, Ala, Gly, Asn, Pro, Gln, or Val;

Xaa at position 36 is Asp, Leu, or Val;
Xaa at position 37 is Phe, Ser, Pro, Trp, or Ile;
Xaa at position 38 is Asn, or Ala;
Xaa at position 40 is Leu, Trp, or Arg;
Xaa at position 41 is Asn, Cys, Arg, Leu, His, Met, or Pro;
Xaa at position 42 is Gly, Asp, Ser, Cys, Asn, Lys, Thr, Leu, Val, Glu, Phe, Tyr, Ile, Met or Ala;
Xaa at position 43 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala, Cys, Gln, Arg, Thr, Gly or Ser;
Xaa at position 44 is Asp, Ser, Leu, Arg, Lys, Thr, Met, Trp, Glu, Asn, Gln, Ala or Pro;
Xaa at position 45 is Gln, Pro, Phe, Val, Met, Leu, Thr, Lys, Trp, Asp, Asn, Arg, Ser, Ala, Ile, Glu or His;
Xaa at position 46 is Asp, Phe, Ser, Thr, Cys, Glu, Asn, Gln, Lys, His, Ala, Tyr, Ile, Val or Gly;
Xaa at position 47 is Ile, Gly, Val, Ser, Arg, Pro, or His;
Xaa at position 48 is Leu, Ser, Cys, Arg, Ile, His, Phe, Glu, Lys, Thr, Ala, Met, Val or Asn;
Xaa at position 49 is Met, Arg, Ala, Gly, Pro, Asn, His, or Asp;
Xaa at position 50 is Glu, Leu, Thr, Asp, Tyr, Lys, Asn, Ser, Ala, Ile, Val, His, Phe, Met or Gln;
Xaa at position 51 is Asn, Arg, Met, Pro, Ser, Thr, or His;
Xaa at position 52 is Asn, His, Arg, Leu, Gly, Ser, or Thr;
Xaa at position 53 is Leu, Thr, Ala, Gly, Glu, Pro, Lys, Ser, or Met;
Xaa at position 54 is Arg, Asp, Ile, Ser, Val, Thr, Gln, Asn, Lys, His, Ala or Leu;
Xaa at position 55 is Arg, Thr, Val, Ser, Leu, or Gly;
Xaa at position 56 is Pro, Gly, Cys, Ser, Gln, Glu, Arg, His, Thr, Ala, Tyr, Phe, Leu, Val or Lys;
Xaa at position 57 is Asn or Gly;
Xaa at position 58 is Leu, Ser, Asp, Arg, Gln, Val, or

Cys;
Xaa at position 59 is Glu Tyr, His, Leu, Pro, or Arg;
Xaa at position 60 is Ala, Ser, Pro, Tyr, Asn, or Thr;
Xaa at position 61 is Phe, Asn, Glu, Pro, Lys, Arg, or Ser;
Xaa at position 62 is Asn His, Val, Arg, Pro, Thr, Asp, or Ile;
Xaa at position 63 is Arg, Tyr, Trp, Lys, Ser, His, Pro, or Val;
Xaa at position 64 is Ala, Asn, Pro, Ser, or Lys;
Xaa at position 65 is Val, Thr, Pro, His, Leu, Phe, or Ser;
Xaa at position 66 is Lys, Ile, Arg, Val, Asn, Glu, or Ser;
Xaa at position 67 is Ser, Ala, Phe, Val, Gly, Asn, Ile, Pro, or His;
Xaa at position 68 is Leu, Val, Trp, Ser, Ile, Phe, Thr, or His;
Xaa at position 69 is Gln, Ala, Pro, Thr, Glu, Arg, Trp, Gly, or Leu;
Xaa at position 70 is Asn, Leu, Val, Trp, Pro, or Ala;
Xaa at position 71 is Ala, Met, Leu, Pro, Arg, Glu, Thr, Gln, Trp, or Asn;
Xaa at position 72 is Ser, Glu, Met, Ala, His, Asn, Arg, or Asp;
Xaa at position 73 is Ala, Glu, Asp, Leu, Ser, Gly, Thr, or Arg;
Xaa at position 74 is Ile, Met, Thr, Pro, Arg, Gly, Ala;
Xaa at position 75 is Glu, Lys, Gly, Asp, Pro, Trp, Arg, Ser, Gln, or Leu;
Xaa at position 76 is Ser, Val, Ala, Asn, Trp, Glu, Pro, Gly, or Asp;
Xaa at position 77 is Ile, Ser, Arg, Thr, or Leu;
Xaa at position 78 is Leu, Ala, Ser, Glu, Phe, Gly, or Arg;
Xaa at position 79 is Lys, Thr, Asn, Met, Arg, Ile, Gly, or Asp;

Xaa at position 80 is Asn, Trp, Val, Gly, Thr, Leu, Glu, or Arg;

Xaa at position 81 is Leu, Gln, Gly, Ala, Trp, Arg, Val, or Lys;

Xaa at position 82 is Leu, Gln, Lys, Trp, Arg, Asp, Glu, Asn, His, Thr, Ser, Ala, Tyr, Phe, Ile, Met or Val;

Xaa at position 83 is Pro, Ala, Thr, Trp, Arg, or Met;

Xaa at position 84 is Cys, Glu, Gly, Arg, Met, or Val;

Xaa at position 85 is Leu, Asn, Val, or Gln;

Xaa at position 86 is Pro, Cys, Arg, Ala, or Lys;

Xaa at position 87 is Leu, Ser, Trp, or Gly;

Xaa at position 88 is Ala, Lys, Arg, Val, or Trp;

Xaa at position 89 is Thr, Asp, Cys, Leu, Val, Glu, His, Asn, or Ser;

Xaa at position 90 is Ala, Pro, Ser, Thr, Gly, Asp, Ile, or Met;

Xaa at position 91 is Ala, Pro, Ser, Thr, Phe, Leu, Asp, or His;

Xaa at position 92 is Pro, Phe, Arg, Ser, Lys, His, Ala, Gly, Ile or Leu;

Xaa at position 93 is Thr, Asp, Ser, Asn, Pro, Ala, Leu, or Arg;

Xaa at position 94 is Arg, Ile, Ser, Glu, Leu, Val, Gln, Lys, His, Ala, or Pro;

Xaa at position 95 is His, Gln, Pro, Arg, Val, Leu, Gly, Thr, Asn, Lys, Ser, Ala, Trp, Phe, Ile, or Tyr;

Xaa at position 96 is Pro, Lys, Tyr, Gly, Ile, or Thr;

Xaa at position 97 is Ile, Val, Lys, Ala, or Asn;

Xaa at position 98 is His, Ile, Asn, Leu, Asp, Ala, Thr, Glu, Gln, Ser, Phe, Met, Val, Lys, Arg, Tyr or Pro;

Xaa at position 99 is Ile, Leu, Arg, Asp, Val, Pro, Gln, Gly, Ser, Phe, or His;

Xaa at position 100 is Lys, Tyr, Leu, His, Arg, Ile, Ser, Gln, or Pro;

Xaa at position 101 is Asp, Pro, Met, Lys, His, Thr, Val, Tyr, Glu, Asn, Ser, Ala, Gly, Ile, Leu, or Gln;

Xaa at position 102 is Gly, Leu, Glu, Lys, Ser, Tyr, or

Pro;

Xaa at position 103 is Asp, or Ser;

Xaa at position 104 is Trp, Val, Cys, Tyr, Thr, Met, Pro, Leu, Gln, Lys, Ala, Phe, or Gly;

Xaa at position 105 is Asn, Pro, Ala, Phe, Ser, Trp, Gln, Tyr, Leu, Lys, Ile, Asp, or His;

Xaa at position 106 is Glu, Ser, Ala, Lys, Thr, Ile, Gly, or Pro;

Xaa at position 108 is Arg, Lys, Asp, Leu, Thr, Ile, Gln, His, Ser, Ala or Pro;

Xaa at position 109 is Arg, Thr, Pro, Glu, Tyr, Leu, Ser, or Gly;

Xaa at position 110 is Lys, Ala, Asn, Thr, Leu, Arg, Gln, His, Glu, Ser, Ala, or Trp;

Xaa at position 111 is Leu, Ile, Arg, Asp, or Met;

Xaa at position 112 is Thr, Val, Gln, Tyr, Glu, His, Ser, or Phe;

Xaa at position 113 is Phe, Ser, Cys, His, Gly, Trp, Tyr, Asp, Lys, Leu, Ile, Val or Asn;

Xaa at position 114 is Tyr, Cys, His, Ser, Trp, Arg, or Leu;

Xaa at position 115 is Leu, Asn, Val, Pro, Arg, Ala, His, Thr, Trp, or Met;

Xaa at position 116 is Lys, Leu, Pro, Thr, Met, Asp, Val, Glu, Arg, Trp, Ser, Asn, His, Ala, Tyr, Phe, Gln, or Ile;

Xaa at position 117 is Thr, Ser, Asn, Ile, Trp, Lys, or Pro;

Xaa at position 118 is Leu, Ser, Pro, Ala, Glu, Cys, Asp, or Tyr;

Xaa at position 119 is Glu, Ser, Lys, Pro, Leu, Thr, Tyr, or Arg;

Xaa at position 120 is Asn, Ala, Pro, Leu, His, Val, or Gln;

Xaa at position 121 is Ala, Ser, Ile, Asn, Pro, Lys, Asp, or Gly;

Xaa at position 122 is Gln, Ser, Met, Trp, Arg, Phe, Pro,

His, Ile, Tyr, or Cys;
Xaa at position 123 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu;

and which can additionally have Met- preceding the amino acid in position 1; and wherein from 1 to 14 amino acids can be deleted from the N-terminus and/or from 1 to 15 amino acids can be deleted from the C-terminus; and wherein from 4 to 44 of the amino acids designated by Xaa are different from the corresponding amino acids of native (1-133) human interleukin-3;

A colony stimulating factor selected from the group consisting of GM-CSF, CSF-1, G-CSF, Meg-CSF (more recently referred to as c-mpl ligand), M-CSF, erythropoietin (EPO), IL-1, IL-4, IL-2, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, LIF, flt3/flk2, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor (SCF); and

At least one non-toxic pharmaceutically acceptable carrier.

2 A composition, comprising: A human interleukin-3 mutant polypeptide of the Formula:

Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn
1 5 10 15

Cys Xaa Xaa Xaa Ile Xaa Glu Xaa Xaa Xaa Xaa Leu Lys Xaa Xaa
20 25 30

Xaa Xaa Xaa Xaa Xaa Asp Xaa Xaa Asn Leu Asn Xaa Glu Xaa Xaa
35 40 45

Xaa Ile Leu Met Xaa Xaa Asn Leu Xaa Xaa Xaa Asn Leu Glu Xaa
50 55 60

Phe Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Ile Glu
65 70 75

Xaa Xaa Leu Xaa Xaa Leu Xaa Xaa Cys Xaa Pro Xaa Xaa Thr Ala
80 85 90

Xaa Pro Xaa Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Asp Xaa Xaa
95 100 105

Xaa Phe Xaa Xaa Lys Leu Xaa Phe Xaa Xaa Xaa Xaa Leu Glu Xaa
110 115 120

Xaa Xaa Xaa Gln Gln Thr Thr Leu Ser Leu Ala Ile Phe
125 130

[SEQ ID NO:2]

wherein
Xaa at position 17 is Ser, Gly, Asp, Met, or Gln;
Xaa at position 18 is Asn, His, or Ile;
Xaa at position 19 is Met or Ile;
Xaa at position 21 is Asp or Glu;
Xaa at position 23 is Ile, Ala, Leu, or Gly;
Xaa at position 24 is Ile, Val, or Leu;
Xaa at position 25 is Thr, His, Gln, or Ala;
Xaa at position 26 is His or Ala;
Xaa at position 29 is Gln, Asn, or Val;
Xaa at position 30 is Pro, Gly, or Gln;
Xaa at position 31 is Pro, Asp, Gly, or Gln;

Xaa at position 32 is Leu, Arg, Gln, Asn, Gly, Ala, or Glu;
Xaa at position 33 is Pro or Glu;
Xaa at position 34 is Leu, Val, Gly, Ser, Lys, Ala, Arg, Gln, Glu, Ile, Phe, Thr or Met;
Xaa at position 35 is Leu, Ala, Asn, Pro, Gln, or Val;
Xaa at position 37 is Phe, Ser, Pro, or Trp;
Xaa at position 38 is Asn or Ala;
Xaa at position 42 is Gly, Asp, Ser, Cys, Ala, Asn, Ile, Leu, Met, Tyr or Arg;
Xaa at position 44 is Asp or Glu;
Xaa at position 45 is Gln, Val, Met, Leu, Thr, Ala, Asn, Glu, Ser or Lys;
Xaa at position 46 is Asp, Phe, Ser, Thr, Ala, Asn Gln, Glu, His, Ile, Lys, Tyr, Val or Cys;
Xaa at position 50 is Glu, Ala, Asn, Ser or Asp;
Xaa at position 51 is Asn, Arg, Met, Pro, Ser, Thr, or His;
Xaa at position 54 is Arg or Ala;
Xaa at position 55 is Arg, Thr, Val, Leu, or Gly;
Xaa at position 56 is Pro, Gly, Ser, Gln, Ala, Arg, Asn, Glu, Leu, Thr, Val or Lys;
Xaa at position 60 is Ala or Ser;
Xaa at position 62 is Asn, Pro, Thr, or Ile;
Xaa at position 63 is Arg or Lys;
Xaa at position 64 is Ala or Asn;
Xaa at position 65 is Val or Thr;
Xaa at position 66 is Lys or Arg;
Xaa at position 67 is Ser, Phe, or His;
Xaa at position 68 is Leu, Ile, Phe, or His;
Xaa at position 69 is Gln, Ala, Pro, Thr, Glu, Arg, or Gly;
Xaa at position 71 is Ala, Pro, or Arg;
Xaa at position 72 is Ser, Glu, Arg, or Asp;
Xaa at position 73 is Ala or Leu;
Xaa at position 76 is Ser, Val, Ala, Asn, Glu, Pro, or Gly;

Xaa at position 77 is Ile or Leu;
Xaa at position 79 is Lys, Thr, Gly, Asn, Met, Arg, Ile, Gly, or Asp;
Xaa at position 80 is Asn, Gly, Glu, or Arg;
Xaa at position 82 is Leu, Gln, Trp, Arg, Asp, Ala, Asn, Glu, His, Ile, Met, Phe, Ser, Thr, Tyr or Val;
Xaa at position 83 is Pro or Thr;
Xaa at position 85 is Leu or Val;
Xaa at position 87 is Leu or Ser;
Xaa at position 88 is Ala or Trp;
Xaa at position 91 is Ala or Pro;
Xaa at position 93 is Thr, Asp, Ser, Pro, Ala, Leu, or Arg;
Xaa at position 95 is His, Pro, Arg, Val, Leu, Gly, Asn, Phe, Ser or Thr;
Xaa at position 96 is Pro or Tyr;
Xaa at position 97 is Ile or Val;
Xaa at position 98 is His, Ile, Asn, Leu, Ala, Thr, Leu, Arg, Gln, Leu, Lys, Met, Ser, Tyr, Val or Pro;
Xaa at position 99 is Ile, Leu, or Val;
Xaa at position 100 is Lys, Arg, Ile, Gln, Pro, or Ser;
Xaa at position 101 is Asp, Pro, Met, Lys, His, Thr, Pro, Asn, Ile, Leu or Tyr;
Xaa at position 104 is Trp or Leu;
Xaa at position 105 is Asn, Pro, Ala, Ser, Trp, Gln, Tyr, Leu, Lys, Ile, Asp, or His;
Xaa at position 106 is Glu or Gly;
Xaa at position 108 is Arg, Ala, or Ser;
Xaa at position 109 is Arg, Thr, Glu, Leu, or Ser;
Xaa at position 112 is Thr, Val, or Gln;
Xaa at position 114 is Tyr or Trp;
Xaa at position 115 is Leu or Ala;
Xaa at position 116 is Lys, Thr, Val, Trp, Ser, Ala, His, Met, Phe, Tyr or Ile;
Xaa at position 117 is Thr or Ser;
Xaa at position 120 is Asn, Pro, Leu, His, Val, or Gln;
Xaa at position 121 is Ala, Ser, Ile, Asn, Pro, Asp, or

Gly;
Xaa at position 122 is Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, or Cys;
Xaa at position 123 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu.

and which can additionally have Met- preceding the amino acid in position 1; and wherein from 1 to 14 amino acids can be deleted from the N-terminus and/or from 1 to 15 amino acids can be deleted from the C-terminus; and wherein from 4 to 35 of the amino acids designated by Xaa are different from the corresponding amino acids of native (1-133)human interleukin-3;

A colony stimulating factor selected from the group consisting of GM-CSF, CSF-1, G-CSF, Meg-CSF (more recently referred to as c-mpl ligand), M-CSF, erythropoietin (EPO), IL-1, IL-4, IL-2, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, LIF, flt3/flk2, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor (SCF); and

At least one non-toxic pharmaceutically acceptable carrier.

3. A composition of 2, wherein said human interleukin-3 mutant polypeptide is of the Formula:

Ala	Pro	Met	Thr	Gln	Thr	Thr	Ser	Leu	Lys	Thr	Ser	Trp	Val	Asn
1				5					10					15

Cys	Xaa	Xaa	Met	Ile	Asp	Glu	Xaa	Ile	Xaa	Xaa	Leu	Lys	Xaa	Xaa
				20					25					30

Pro Xaa Pro Xaa Xaa Asp Phe Xaa Asn Leu Asn Xaa Glu Asp Xaa
35 40 45

Xaa Ile Leu Met Xaa Xaa Asn Leu Arg Xaa Xaa Asn Leu Glu Ala
50 55 60

Phe Xaa Arg Xaa Xaa Lys Xaa Xaa Xaa Asn Ala Ser Ala Ile Glu
65 70 75

Xaa Xaa Leu Xaa Xaa Leu Xaa Pro Cys Leu Pro Xaa Xaa Thr Ala
80 85 90

Xaa Pro Xaa Arg Xaa Pro Ile Xaa Xaa Xaa Xaa Gly Asp Trp Xaa
95 100 105

Glu Phe Xaa Xaa Lys Leu Xaa Phe Tyr Leu Xaa Xaa Leu Glu Xaa
110 115 120

Xaa Xaa Xaa Gln Gln Thr Thr Leu Ser Leu Ala Ile Phe
125 130

[SEQ ID NO:3]

wherein
Xaa at position 17 is Ser, Gly, Asp, or Gln;
Xaa at position 18 is Asn, His, or Ile;
Xaa at position 23 is Ile, Ala, Leu, or Gly;
Xaa at position 25 is Thr, His, or Gln;
Xaa at position 26 is His or Ala;
Xaa at position 29 is Gln or Asn;
Xaa at position 30 is Pro or Gly;
Xaa at position 32 is Leu, Arg, Asn, or Ala;
Xaa at position 34 is Leu, Val, Ser, Ala, Arg, Gln, Glu, Ile, Phe, Thr, or Met;
Xaa at position 35 is Leu, Ala, Asn, or Pro;
Xaa at position 38 is Asn or Ala;
Xaa at position 42 is Gly, Asp, Ser, Ala, Asn, Ile, Leu, Met, Tyr or Arg;

Xaa at position 45 is Gln, Val, Met, Leu, Ala, Asn, Glu, or Lys;

Xaa at position 46 is Asp, Phe, Ser, Gln, Glu, His, Val or Thr;

Xaa at position 50 is Glu Asn, Ser or Asp;

Xaa at position 51 is Asn, Arg, Pro, Thr, or His;

Xaa at position 55 is Arg, Leu, or Gly;

Xaa at position 56 is Pro, Gly, Ser, Ala, Asn, Val, Leu or Gln;

Xaa at position 62 is Asn, Pro, or Thr;

Xaa at position 64 is Ala or Asn;

Xaa at position 65 is Val or Thr;

Xaa at position 67 is Ser or Phe;

Xaa at position 68 is Leu or Phe;

Xaa at position 69 is Gln, Ala, Glu, or Arg;

Xaa at position 76 is Ser, Val, Asn, Pro, or Gly;

Xaa at position 77 is Ile or Leu;

Xaa at position 79 is Lys, Gly, Asn, Met, Arg, Ile, or Gly;

Xaa at position 80 is Asn, Gly, Glu, or Arg;

Xaa at position 82 is Leu, Gln, Trp, Arg, Asp, Asn, Glu, His, Met, Phe, Ser, Thr, Tyr or Val;

Xaa at position 87 is Leu or Ser;

Xaa at position 88 is Ala or Trp;

Xaa at position 91 is Ala or Pro;

Xaa at position 93 is Thr, Asp, or Ala;

Xaa at position 95 is His, Pro, Arg, Val, Gly, Asn, Ser or Thr;

Xaa at position 98 is His, Ile, Asn, Ala, Thr, Gln, Glu, Lys, Met, Ser, Tyr, Val or Leu;

Xaa at position 99 is Ile or Leu;

Xaa at position 100 is Lys or Arg;

Xaa at position 101 is Asp, Pro, Met, Lys, Thr, His, Pro, Asn, Ile, Leu or Tyr;

Xaa at position 105 is Asn, Pro, Ser, Ile or Asp;

Xaa at position 108 is Arg, Ala, or Ser;

Xaa at position 109 is Arg, Thr, Glu, Leu, or Ser;

Xaa at position 112 is Thr or Gln;
Xaa at position 116 is Lys, Val, Trp, Ala, His, Phe, Tyr or Ile;
Xaa at position 117 is Thr or Ser;
Xaa at position 120 is Asn, Pro, Leu, His, Val, or Gln;
Xaa at position 121 is Ala, Ser, Ile, Pro, or Asp;
Xaa at position 122 is Gln, Met, Trp, Phe, Pro, His, Ile, or Tyr;
Xaa at position 123 is Ala, Met, Glu, Ser, or Leu;

and which can additionally have Met- preceding the amino acid in position 1; and wherein from 1 to 14 amino acids can be deleted from the N-terminus and/or from 1 to 15 amino acids can be deleted from the C-terminus; and wherein from 4 to 44 of the amino acids designated by Xaa are different from the corresponding amino acids of native (1-133)human interleukin-3.

4. A composition of 3,wherein said human interleukin-3 mutant polypeptide is of the Formula:

Xaa at position 42 is Gly, Asp, Ser, Ile, Leu, Met, Tyr, or Ala;
Xaa at position 45 is Gln, Val, Met or Asn;
Xaa at position 46 is Asp, Ser, Gln, His or Val;
Xaa at position 50 is Glu or Asp;
Xaa at position 51 is Asn, Pro or Thr;
Xaa at position 62 is Asn or Pro;
Xaa at position 76 is Ser, or Pro;
Xaa at position 82 is Leu, Trp, Asp, Asn Glu, His, Phe, Ser or Tyr;
Xaa at position 95 is His, Arg, Thr, Asn or Ser;
Xaa at position 98 is His, Ile, Leu, Ala, Gln, Lys, Met, Ser, Tyr or Val;
Xaa at position 100 is Lys or Arg;

Xaa at position 101 is Asp, Pro, His, Asn, Ile or Leu;
Xaa at position 105 is Asn, or Pro;
Xaa at position 108 is Arg, Ala, or Ser;
Xaa at position 116 is Lys, Val, Trp, Ala, His, Phe, or Tyr;
Xaa at position 121 is Ala, or Ile;
Xaa at position 122 is Gln, or Ile; and
Xaa at position 123 is Ala, Met or Glu.

5. A composition, comprising:

A human interleukin-3 mutant polypeptide of the Formula:

Asn Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Xaa Xaa
20 25 30

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
35 40 45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
50 55 60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
80 85 90

Xaa Xaa Phe Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
95 100 105

Xaa Xaa Xaa Xaa Gln Gln [SEQ ID NO:4]
110

wherein

Xaa at position 3 is Ser, Lys, Gly, Asp, Met, Gln, or Arg;

Xaa at position 4 is Asn, His, Leu, Ile, Phe, Arg, or Gln;

Xaa at position 5 is Met, Phe, Ile, Arg, Gly, Ala, or Cys;

Xaa at position 6 is Ile, Cys, Gln, Glu, Arg, Pro, or Ala;

Xaa at position 7 is Asp, Phe, Lys, Arg, Ala, Gly, Glu, Gln, Asn, Thr, Ser or Val;

Xaa at position 8 is Glu, Trp, Pro, Ser, Ala, His, Asp, Asn, Gln, Leu, Val, or Gly;

Xaa at position 9 is Ile, Val, Ala, Leu, Gly, Trp, Lys, Phe, Leu, Ser, or Arg;

Xaa at position 10 is Ile, Gly, Val, Arg, Ser, Phe, or Leu;

Xaa at position 11 is Thr, His, Gly, Gln, Arg, Pro, or Ala;

Xaa at position 12 is His, Thr, Phe, Gly, Arg, Ala, or Trp;

Xaa at position 13 is Leu, Gly, Arg, Thr, Ser, or Ala;

Xaa at position 14 is Lys, Arg, Leu, Gln, Gly, Pro, Val or Trp;

Xaa at position 15 is Gln, Asn, Leu, Pro, Arg, or Val;

Xaa at position 16 is Pro, His, Thr, Gly, Asp, Gln, Ser, Leu, or Lys;

Xaa at position 17 is Pro, Asp, Gly, Ala, Arg, Leu, or Gln;

Xaa at position 18 is Leu, Val, Arg, Gln, Asn, Gly, Ala, or Glu;

Xaa at position 19 is Pro, Leu, Gln, Ala, Thr, or Glu;

Xaa at position 20 is Leu, Val, Gly, Ser, Lys, Glu, Gln, Thr, Arg, Ala, Phe, Ile or Met;

Xaa at position 21 is Leu, Ala, Gly, Asn, Pro, Gln, or Val;

Xaa at position 22 is Asp, Leu, or Val;

Xaa at position 23 is Phe, Ser, Pro, Trp, or Ile;

Xaa at position 24 is Asn, or Ala;

Xaa at position 26 is Leu, Trp, or Arg;

Xaa at position 27 is Asn, Cys, Arg, Leu, His, Met, Pro;

Xaa at position 28 is Gly, Asp, Ser, Cys, Ala, Lys, Asn, Thr, Leu, Val, Glu, Phe, Tyr, Ile or Met;

Xaa at position 29 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala, Cys, Gln, Arg, Thr, Gly or Ser;

Xaa at position 30 is Asp, Ser, Leu, Arg, Lys, Thr,Met, Trp, Glu, Asn, Gln, Ala or Pro;

Xaa at position 31 is Gln, Pro, Phe, Val, Met, Leu, Thr, Lys, Asp, Asn, Arg, Ser, Ala, Ile, Glu, His or Trp;

Xaa at position 32 is Asp, Phe, Ser, Thr, Cys, Glu, Asn, Gln, Lys, His, Ala, Tyr, Ile, Val or Gly;

Xaa at position 33 is Ile, Gly, Val, Ser, Arg, Pro, or His;

Xaa at position 34 is Leu, Ser, Cys, Arg, Ile, His, Phe, Glu, Lys, Thr, Ala, Met, Val or Asn;

Xaa at position 35 is Met, Arg, Ala, Gly, Pro, Asn, His, or Asp;

Xaa at position 36 is Glu, Leu, Thr, Asp, Tyr, Lys, Asn, Ser, Ala, Ile, Val, His, Phe, Met or Gln;

Xaa at position 37 is Asn, Arg, Met, Pro, Ser, Thr, or His;

Xaa at position 38 is Asn, His, Arg, Leu, Gly, Ser, or Thr;

Xaa at position 39 is Leu, Thr, Ala, Gly, Glu, Pro, Lys, Ser, Met, or;

Xaa at position 40 is Arg, Asp, Ile, Ser, Val, Thr, Gln, Asn, Lys, His, Ala or Leu;

Xaa at position 41 is Arg, Thr, Val, Ser, Leu, or Gly;

Xaa at position 42 is Pro, Gly, Cys, Ser, Gln, Glu, Arg, His, Thr, Ala, Tyr, Phe, Leu, Val or Lys;

Xaa at position 43 is Asn or Gly;

Xaa at position 44 is Leu, Ser, Asp, Arg, Gln, Val, or Cys;

Xaa at position 45 is Glu Tyr, His, Leu, Pro, or Arg;

Xaa at position 46 is Ala, Ser, Pro, Tyr, Asn, or Thr;

Xaa at position 47 is Phe, Asn, Glu, Pro, Lys, Arg, or Ser;

Xaa at position 48 is Asn, His, Val, Arg, Pro, Thr, Asp,

or Ile;
Xaa at position 49 is Arg, Tyr, Trp, Lys, Ser, His, Pro, or Val;
Xaa at position 50 is Ala, Asn, Pro, Ser, or Lys;
Xaa at position 51 is Val, Thr, Pro, His, Leu, Phe, or Ser;
Xaa at position 52 is Lys, Ile, Arg, Val, Asn, Glu, or Ser;
Xaa at position 53 is Ser, Ala, Phe, Val, Gly, Asn, Ile, Pro, or His;
Xaa at position 54 is Leu, Val, Trp, Ser, Ile, Phe, Thr, or His;
Xaa at position 55 is Gln, Ala, Pro, Thr, Glu, Arg, Trp, Gly, or Leu;
Xaa at position 56 is Asn, Leu, Val, Trp, Pro, or Ala;
Xaa at position 57 is Ala, Met, Leu, Pro, Arg, Glu, Thr, Gln, Trp, or Asn;
Xaa at position 58 is Ser, Glu, Met, Ala, His, Asn, Arg, or Asp;
Xaa at position 59 is Ala, Glu, Asp, Leu, Ser, Gly, Thr, or Arg;
Xaa at position 60 is Ile, Met, Thr, Pro, Arg, Gly, Ala;
Xaa at position 61 is Glu, Lys, Gly, Asp, Pro, Trp, Arg, Ser, Gln, or Leu;
Xaa at position 62 is Ser, Val, Ala, Asn, Trp, Glu, Pro, Gly, or Asp;
Xaa at position 63 is Ile, Ser, Arg, Thr, or Leu;
Xaa at position 64 is Leu, Ala, Ser, Glu, Phe, Gly, or Arg;
Xaa at position 65 is Lys, Thr, Gly, Asn, Met, Arg, Ile, or Asp;
Xaa at position 66 is Asn, Trp, Val, Gly, Thr, Leu, Glu, or Arg;
Xaa at position 67 is Leu, Gln, Gly, Ala, Trp, Arg, Val, or Lys;
Xaa at position 68 is Leu, Gln, Lys, Trp, Arg, Asp, Glu, Asn, His, Thr, Ser, Ala, Tyr, Phe, Ile, Met or Val;

Xaa at position 69 is Pro, Ala, Thr, Trp, Arg, or Met;
Xaa at position 70 is Cys, Glu, Gly, Arg, Met, or Val;
Xaa at position 71 is Leu, Asn, Val, or Gln;
Xaa at position 72 is Pro, Cys, Arg, Ala, or Lys;
Xaa at position 73 is Leu, Ser, Trp, or Gly;
Xaa at position 74 is Ala, Lys, Arg, Val, or Trp;
Xaa at position 75 is Thr, Asp, Cys, Leu, Val, Glu, His, Asn, or Ser;
Xaa at position 76 is Ala, Pro, Ser, Thr, Gly, Asp, Ile, or Met;
Xaa at position 77 is Ala, Pro, Ser, Thr, Phe, Leu, Asp, or His;
Xaa at position 78 is Pro, Phe, Arg, Ser, Lys, His, Ala, Gly, Ile or Leu;
Xaa at position 79 is Thr, Asp, Ser, Asn, Pro, Ala, Leu, or Arg;
Xaa at position 80 is Arg, Ile, Ser, Glu, Leu, Val, Gln, Lys, His, Ala or Pro;
Xaa at position 81 is His, Gln, Pro, Arg, Val, Leu, Gly, Thr, Asn, Lys, Ser, Ala, Trp, Phe, Ile or Tyr;
Xaa at position 82 is Pro, Lys, Tyr, Gly, Ile, or Thr;
Xaa at position 83 is Ile, Val, Lys, Ala, or Asn;
Xaa at position 84 is His, Ile, Asn, Leu, Asp, Ala, Thr, Glu, Gln, Ser, Phe, Met, Val, Lys, Arg, Tyr or Pro;
Xaa at position 85 is Ile, Leu, Arg, Asp, Val, Pro, Gln, Gly, Ser, Phe, or His;
Xaa at position 86 is Lys, Tyr, Leu, His, Arg, Ile, Ser, Gln, Pro;
Xaa at position 87 is Asp, Pro, Met, Lys, His, Thr, Val, Tyr, Glu, Asn, Ser, Ala, Gly, Ile, Leu or Gln;
Xaa at position 88 is Gly, Leu, Glu, Lys, Ser, Tyr, or Pro;
Xaa at position 89 is Asp, or Ser;
Xaa at position 90 is Trp, Val, Cys, Tyr, Thr, Met, Pro, Leu, Gln, Lys, Ala, Phe, or Gly;
Xaa at position 91 is Asn, Pro, Ala, Phe, Ser, Trp, Gln, Tyr, Leu, Lys, Ile, Asp, or His;

Xaa at position 92 is Glu, Ser, Ala, Lys, Thr, Ile, Gly, or Pro;

Xaa at position 94 is Arg, Lys, Asp, Leu, Thr, Ile, Gln, His, Ser, Ala, or Pro;

Xaa at position 95 is Arg, Thr, Pro, Glu, Tyr, Leu, Ser, or Gly;

Xaa at position 96 is Lys, Asn, Thr, Leu, Gln, Arg, His, Glu, Ser, Ala or Trp;

Xaa at position 97 is Leu, Ile, Arg, Asp, or Met;

Xaa at position 98 is Thr, Val, Gln, Tyr, Glu, His, Ser, or Phe;

Xaa at position 99 is Phe, Ser, Cys, His, Gly, Trp, Tyr, Asp, Lys, Leu, Ile, Val or Asn;

Xaa at position 100 is Tyr, Cys, His, Ser, Trp, Arg, or Leu;

Xaa at position 101 is Leu, Asn, Val, Pro, Arg, Ala, His, Thr, Trp, or Met;

Xaa at position 102 is Lys, Leu, Pro, Thr, Met, Asp, Val, Glu, Arg, Trp, Ser, Asn, His, Ala, Tyr, Phe, Gln, or Ile;

Xaa at position 103 is Thr, Ser, Asn, Ile, Trp, Lys, or Pro;

Xaa at position 104 is Leu, Ser, Pro, Ala, Glu, Cys, Asp, or Tyr;

Xaa at position 105 is Glu, Ser, Lys, Pro, Leu, Thr, Tyr, or Arg;

Xaa at position 106 is Asn, Ala, Pro, Leu, His, Val, or Gln;

Xaa at position 107 is Ala, Ser, Ile, Asn, Pro, Lys, Asp, or Gly;

Xaa at position 108 is Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, or Cys;

Xaa at position 109 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu;

and which can additionally have Met- or Met-Ala- preceding the amino acid in position 1; and

wherein from 4 to 44 of the amino acids designated by Xaa are different from the corresponding native amino acids of (1-133) human interleukin-3;

A colony stimulating factor selected from the group consisting of GM-CSF, CSF-1, G-CSF, Meg-CSF (more recently referred to as c-mpl ligand), M-CSF, erythropoietin (EPO), IL-1, IL-4, IL-2, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, LIF, flt3/flk2, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor and stem cell factor (SCF); and

At least one non-toxic pharmaceutically acceptable carrier.

6. A composition of 5, wherein said human interleukin-3 mutant polypeptide is of the Formula:

Asn Cys Xaa Xaa Xaa Ile Xaa Glu Xaa Xaa Xaa Xaa Leu Lys Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Xaa Asp Xaa Xaa Asn Leu Asn Xaa Glu Xaa
20 25 30

Xaa Xaa Ile Leu Met Xaa Xaa Asn Leu Xaa Xaa Xaa Asn Leu Glu
35 40 45

Xaa Phe Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Ile
50 55 60

Glu Xaa Xaa Leu Xaa Xaa Leu Xaa Xaa Cys Xaa Pro Xaa Xaa Thr
65 70 75

Ala Xaa Pro Xaa Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Asp Xaa

50

80 85 90

Xaa Xaa Phe Xaa Xaa Lys Leu Xaa Phe Xaa Xaa Xaa Xaa Leu Glu
95 100 105

Xaa Xaa Xaa Xaa Gln Gln [SEQ ID NO:5]
110

wherein
Xaa at position 3 is Ser, Gly, Asp, Met, or Gln;
Xaa at position 4 is Asn, His, or Ile;
Xaa at position 5 is Met or Ile;
Xaa at position 7 is Asp or Glu;
Xaa at position 9 is Ile, Ala, Leu, or Gly;
Xaa at position 10 is Ile, Val, or Leu;
Xaa at position 11 is Thr, His, Gln, or Ala;
Xaa at position 12 is His or Ala;
Xaa at position 15 is Gln, Asn, or Val;
Xaa at position 16 is Pro, Gly, or Gln;
Xaa at position 17 is Pro, Asp, Gly, or Gln;
Xaa at position 18 is Leu, Arg, Gln, Asn, Gly, Ala, or Glu;
Xaa at position 19 is Pro or Glu;
Xaa at position 20 is Leu, Val, Gly, Ser, Lys, Ala, Arg, Gln, Glu, Ile, Phe, Thr or Met;
Xaa at position 21 is Leu, Ala, Asn, Pro, Gln, or Val;
Xaa at position 23 is Phe, Ser, Pro, or Trp;
Xaa at position 24 is Asn or Ala;
Xaa at position 28 is Gly, Asp, Ser, Cys, Ala, Asn, Ile, Leu, Met Tyr or Arg;
Xaa at position 30 is Asp or Glu;
Xaa at position 31 is Gln, Val, Met, Leu, Thr, Ala, Asn, Glu, Ser or Lys;
Xaa at position 32 is Asp, Phe, Ser, Thr, Ala, Asn, Gln, Glu, His, Ile, Lys, Tyr, Val or Cys;
Xaa at position 36 is Glu, Ala, Asn, Ser or Asp;
Xaa at position 37 is Asn, Arg, Met, Pro, Ser, Thr, or

His;

Xaa at position 40 is Arg or Ala;

Xaa at position 41 is Arg, Thr, Val, Leu, or Gly;

Xaa at position 42 is Pro, Gly, Ser, Gln, Ala, Arg, Asn, Glu, Leu, Thr, Val or Lys;

Xaa at position 46 is Ala or Ser;

Xaa at position 48 is Asn, Pro, Thr, or Ile;

Xaa at position 49 is Arg or Lys;

Xaa at position 50 is Ala or Asn;

Xaa at position 51 is Val or Thr;

Xaa at position 52 is Lys or Arg;

Xaa at position 53 is Ser, Phe, or His;

Xaa at position 54 is Leu, Ile, Phe, or His;

Xaa at position 55 is Gln, Ala, Pro, Thr, Glu, Arg, or Gly;

Xaa at position 57 is Ala, Pro, or Arg;

Xaa at position 58 is Ser, Glu, Arg, or Asp;

Xaa at position 59 is Ala or Leu;

Xaa at position 62 is Ser, Val, Ala, Asn, Glu, Pro, or Gly;

Xaa at position 63 is Ile or Leu;

Xaa at position 65 is Lys, Thr, Gly, Asn, Met, Arg, Ile, Gly, or Asp;

Xaa at position 66 is Asn, Gly, Glu, or Arg;

Xaa at position 68 is Leu, Gln, Trp, Arg, Asp, Ala, Asn, Glu, His, Ile, Met, Phe, Ser, Thr, Tyr or Val;

Xaa at position 69 is Pro or Thr;

Xaa at position 71 is Leu or Val;

Xaa at position 73 is Leu or Ser;

Xaa at position 74 is Ala or Trp;

Xaa at position 77 is Ala or Pro;

Xaa at position 79 is Thr, Asp, Ser, Pro, Ala, Leu, or Arg;

Xaa at position 81 is His, Pro, Arg, Val, Leu, Gly, Asn, Phe, Ser or Thr;

Xaa at position 82 is Pro or Tyr;

Xaa at position 83 is Ile or Val;

Xaa at position 84 is His, Ile, Asn, Leu, Ala, Thr, Leu, Arg, Gln, Leu, Lys, Met, Ser, Tyr, Val or Pro;
Xaa at position 85 is Ile, Leu, or Val;
Xaa at position 86 is Lys, Arg, Ile, Gln, Pro, or Ser;
Xaa at position 87 is Asp, Pro, Met, Lys, His, Thr, Asn, Ile, Leu or Tyr;
Xaa at position 90 is Trp or Leu;
Xaa at position 91 is Asn, Pro, Ala, Ser, Trp, Gln, Tyr, Leu, Lys, Ile, Asp, or His;
Xaa at position 92 is Glu, or Gly;
Xaa at position 94 is Arg, Ala, or Ser;
Xaa at position 95 is Arg, Thr, Glu, Leu, or Ser;
Xaa at position 98 is Thr, Val, or Gln;
Xaa at position 100 is Tyr or Trp;
Xaa at position 101 is Leu or Ala;
Xaa at position 102 is Lys, Thr, Val, Trp, Ser, Ala, His, Met, Phe, Tyr or Ile;
Xaa at position 103 is Thr or Ser;
Xaa at position 106 is Asn, Pro, Leu, His, Val, or Gln;
Xaa at position 107 is Ala, Ser, Ile, Asn, Pro, Asp, or Gly;
Xaa at position 108 is Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, or Cys;
Xaa at position 109 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu;

which can additionally have Met- or Met-Ala- preceding the amino acid in position 1; and wherein from 4 to 35 of the amino acids designated by Xaa are different from the corresponding amino acids of native human interleukin-3.

7. A composition of 6, wherein said human interleukin-3 mutant polypeptide is of the Formula:

Asn Cys Xaa Xaa Met Ile Asp Glu Xaa Ile Xaa Xaa Leu Lys Xaa
1 5 10 15

Xaa Pro Xaa Pro Xaa Xaa Asp Phe Xaa Asn Leu Asn Xaa Glu Asp
20 25 30

Xaa Xaa Ile Leu Met Xaa Xaa Asn Leu Arg Xaa Xaa Asn Leu Glu
35 40 45

Ala Phe Xaa Arg Xaa Xaa Lys Xaa Xaa Xaa Asn Ala Ser Ala Ile
50 55 60

Glu Xaa Xaa Leu Xaa Xaa Leu Xaa Pro Cys Leu Pro Xaa Xaa Thr
65 70 75

Ala Xaa Pro Xaa Arg Xaa Pro Ile Xaa Xaa Xaa Xaa Gly Asp Trp
80 85 90

Xaa Glu Phe Xaa Xaa Lys Leu Xaa Phe Tyr Leu Xaa Xaa Leu Glu
95 100 105

Xaa Xaa Xaa Xaa Gln Gln [SEQ ID NO:6]
110

wherein
Xaa at position 3 is Ser, Gly, Asp, or Gln;
Xaa at position 4 is Asn, His, or Ile;
Xaa at position 9 is Ile, Ala, Leu, or Gly;
Xaa at position 11 is Thr, His, or Gln;
Xaa at position 12 is His or Ala;
Xaa at position 15 is Gln or Asn;
Xaa at position 16 is Pro or Gly;
Xaa at position 18 is Leu, Arg, Asn, or Ala;
Xaa at position 20 is Leu, Val, Ser, Ala, Arg, Gln, Glu, Ile, Phe, Thr or Met;
Xaa at position 21 is Leu, Ala, Asn, or Pro;
Xaa at position 24 is Asn or Ala;

Xaa at position 28 is Gly, Asp, Ser, Ala, Asn, Ile, Leu, Met, Tyr or Arg;

Xaa at position 31 is Gln, Val, Met, Leu, Ala, Asn, Glu or Lys;

Xaa at position 32 is Asp, Phe, Ser, Ala, Gln, Glu, His, Val or Thr;

Xaa at position 36 is Glu, Asn, Ser or Asp;

Xaa at position 37 is Asn, Arg, Pro, Thr, or His;

Xaa at position 41 is Arg, Leu, or Gly;

Xaa at position 42 is Pro, Gly, Ser, Ala, Asn, Val, Leu or Gln;

Xaa at position 48 is Asn, Pro, or Thr;

Xaa at position 50 is Ala or Asn;

Xaa at position 51 is Val or Thr;

Xaa at position 53 is Ser or Phe;

Xaa at position 54 is Leu or Phe;

Xaa at position 55 is Gln, Ala, Glu, or Arg;

Xaa at position 62 is Ser, Val, Asn, Pro, or Gly;

Xaa at position 63 is Ile or Leu;

Xaa at position 65 is Lys, Asn, Met, Arg, Ile, or Gly;

Xaa at position 66 is Asn, Gly, Glu, or Arg;

Xaa at position 68 is Leu, Gln, Trp, Arg, Asp, Asn, Glu, His, Met, Phe, Ser, Thr, Tyr or Val;

Xaa at position 73 is Leu or Ser;

Xaa at position 74 is Ala or Trp;

Xaa at position 77 is Ala or Pro;

Xaa at position 79 is Thr, Asp, or Ala;

Xaa at position 81 is His, Pro, Arg, Val, Gly, Asn, Ser or Thr;

Xaa at position 84 is His, Ile, Asn, Ala, Thr, Arg, Gln, Glu, Lys, Met, Ser, Tyr, Val or Leu;

Xaa at position 85 is Ile or Leu;

Xaa at position 86 is Lys or Arg;

Xaa at position 87 is Asp, Pro, Met, Lys, His, Pro, Asn, Ile, Leu or Tyr;

Xaa at position 91 is Asn, Pro, Ser, Ile or Asp;

Xaa at position 94 is Arg, Ala, or Ser;

Xaa at position 95 is Arg, Thr, Glu, Leu, or Ser;
Xaa at position 98 is Thr or Gln;
Xaa at position 102 is Lys, Val, Trp, or Ile;
Xaa at position 103 is Thr, Ala, His, Phe, Tyr or Ser;
Xaa at position 106 is Asn, Pro, Leu, His, Val, or Gln;
Xaa at position 107 is Ala, Ser, Ile, Pro, or Asp;
Xaa at position 108 is Gln, Met, Trp, Phe, Pro, His, Ile, or Tyr;
Xaa at position 109 is Ala, Met, Glu, Ser, or Leu;

and which can additionally have Met- or Met-Ala- preceding the amino acid in position 1; and wherein from 4 to 26 of the amino acids designated by Xaa are different from the corresponding amino acids of native (1-133)human interleukin-3.

8. The composition of 7, wherein said human interleukin-3 mutant polypeptide is of the Formula:

Xaa at position 17 is Ser, Lys, Asp, Met, Gln, or Arg;
Xaa at position 18 is Asn, His, Leu, Ile, Phe, Arg, or \ Gln;
Xaa at position 19 is Met, Arg, Gly, Ala, or Cys;
Xaa at position 20 is Ile, Cys, Gln, Glu, Arg, Pro, or Ala;
Xaa at position 21 is Asp, Phe, Lys, Arg, Ala, Gly, or Val;
Xaa at position 22 is Glu, Trp, Pro, Ser, Ala, His, or Gly;
Xaa at position 23 is Ile, Ala, Gly, Trp, Lys, Leu, Ser, or Arg;
Xaa at position 24 is Ile, Gly, Arg, or Ser;
Xaa at position 25 is Thr, His, Gly, Gln, Arg, Pro, or Ala;
Xaa at position 26 is His, Thr, Phe, Gly, Ala, or Trp;

Xaa at position 27 is Leu, Gly, Arg, Thr, Ser, or Ala;
Xaa at position 28 is Lys, Leu, Gln, Gly, Pro, Val or Trp;
Xaa at position 29 is Gln, Asn, Pro, Arg, or Val;
Xaa at position 30 is Pro, His, Thr, Gly, Asp, Gln, Ser, Leu, or Lys;
Xaa at position 31 is Pro, Asp, Gly, Arg, Leu, or Gln;
Xaa at position 32 is Leu, Arg, Gln, Asn, Gly, Ala, or Glu;
Xaa at position 33 is Pro, Leu, Gln, Thr, or Glu;
Xaa at position 34 is Leu, Gly, Ser, or Lys;
Xaa at position 35 is Leu, Ala, Gly, Asn, Pro, or Gln;
Xaa at position 36 is Asp, Leu, or Val;
Xaa at position 37 is Phe, Ser, or Pro;
Xaa at position 38 is Asn, or Ala;
Xaa at position 40 is Leu, Trp, or Arg;
Xaa at position 41 is Asn, Cys, Arg, Leu, His, Met, Pro;
Xaa at position 42 is Gly, Asp, Ser, Cys, or Ala;
Xaa at position 42 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala, Cys, or Ser;
Xaa at position 44 is Asp, Ser, Leu, Arg, Lys, Thr, Met, Trp, or Pro;
Xaa at position 45 is Gln, Pro, Phe, Val, Met, Leu, Thr, Lys, or Trp;
Xaa at position 46 is Asp, Phe, Ser, Thr, Cys, or Gly;
Xaa at position 47 is Ile, Gly, Ser, Arg, Pro, or His;
Xaa at position 48 is Leu, Ser, Cys, Arg, His, Phe, or Asn;
Xaa at position 49 is Met, Arg, Ala, Gly, Pro, Asn, His, or Asp;
Xaa at position 50 is Glu, Leu, Thr, Asp, or Tyr;
Xaa at position 51 is Asn, Arg, Met, Pro, Ser, Thr, or His;
Xaa at position 52 is Asn, His, Arg, Leu, Gly, Ser, or Thr;
Xaa at position 53 is Leu, Thr, Ala, Gly, Glu, Pro, Lys, Ser, or;
Xaa at position 54 is Arg, Asp, Ile, Ser, Val, Thr, Gln,

or Leu;

Xaa at position 55 is Arg, Thr, Val, Ser, Leu, or Gly;

Xaa at position 56 is Pro, Gly, Cys, Ser, Gln, or Lys;

Xaa at position 57 is Asn or Gly;

Xaa at position 58 is Leu, Ser, Asp, Arg, Gln, Val, or Cys;

Xaa at position 59 is Glu Tyr, His, Leu, Pro, or Arg;

Xaa at position 60 is Ala, Ser, Tyr, Asn, or Thr;

Xaa at position 61 is Phe, Asn, Glu, Pro, Lys, Arg, or Ser;

Xaa at position 62 is Asn His, Val, Arg, Pro, Thr, or Ile;

Xaa at position 63 is Arg, Tyr, Trp, Ser, Pro, or Val;

Xaa at position 64 is Ala, Asn, Ser, or Lys;

Xaa at position 65 is Val, Thr, Pro, His, Leu, Phe, or Ser;

Xaa at position 66 is Lys, Ile, Val, Asn, Glu, or Ser;

Xaa at position 67 is Ser, Ala, Phe, Val, Gly, Asn, Ile, Pro, or His;

Xaa at position 68 is Leu, Val, Trp, Ser, Thr, or His;

Xaa at position 69 is Gln, Ala, Pro, Thr, Arg, Trp, Gly, or Leu;

Xaa at position 70 is Asn, Leu, Val, Trp, Pro, or Ala;

Xaa at position 71 is Ala, Met, Leu, Arg, Glu, Thr, Gln, Trp, or Asn;

Xaa at position 72 is Ser, Glu, Met, Ala, His, Asn, Arg, or Asp;

Xaa at position 73 is Ala, Glu, Asp, Leu, Ser, Gly, Thr, or Arg;

Xaa at position 74 is Ile, Thr, Pro, Arg, Gly, Ala;

Xaa at position 75 is Glu, Lys, Gly, Asp, Pro, Trp, Arg, Ser, or Leu;

Xaa at position 76 is Ser, Val, Ala, Asn, Trp, Glu, Pro, Gly, or Asp;

Xaa at position 77 is Ile, Ser, Arg, or Thr;

Xaa at position 78 is Leu, Ala, Ser, Glu, Gly, or Arg;

Xaa at position 79 is Lys, Thr, Gly, Asn, Met, Ile, or Asp;

Xaa at position 80 is Asn, Trp, Val, Gly, Thr, Leu, or Arg;

Xaa at position 81 is Leu, Gln, Gly, Ala, Trp, Arg, or Lys;

Xaa at position 82 is Leu, Gln, Lys, Trp, Arg, or Asp;

Xaa at position 83 is Pro, Thr, Trp, Arg, or Met;

Xaa at position 84 is Cys, Glu, Gly, Arg, Met, or Val;

Xaa at position 85 is Leu, Asn, or Gln;

Xaa at position 86 is Pro, Cys, Arg, Ala, or Lys;

Xaa at position 87 is Leu, Ser, Trp, or Gly;

Xaa at position 88 is Ala, Lys, Arg, Val, or Trp;

Xaa at position 89 is Thr, Asp, Cys, Leu, Val, Glu, His, or Asn;

Xaa at position 90 is Ala, Ser, Asp, Ile, or Met;

Xaa at position 91 is Ala, Ser, Thr, Phe, Leu, Asp, or His;

Xaa at position 92 is Pro, Phe, Arg, Ser, Lys, His, or Leu;

Xaa at position 93 is Thr, Asp, Ser, Asn, Pro, Ala, Leu, or Arg;

Xaa at position 94 is Arg, Ile, Ser, Glu, Leu, Val, or Pro;

Xaa at position 95 is His, Gln, Pro, Val, Leu, Thr or Tyr;

Xaa at position 96 is Pro, Lys, Tyr, Gly, Ile, or Thr;

Xaa at position 97 is Ile, Lys, Ala, or Asn;

Xaa at position 98 is His, Ile, Asn, Leu, Asp, Ala, Thr, or Pro;

Xaa at position 99 is Ile, Arg, Asp, Pro, Gln, Gly, Phe, or His;

Xaa at position 100 is Lys, Tyr, Leu, His, Ile, Ser, Gln, or Pro;

Xaa at position 101 is Asp, Pro, Met, Lys, His, Thr, Val, Tyr, or Gln;

Xaa at position 102 is Gly, Leu, Glu, Lys, Ser, Tyr, or Pro;

Xaa at position 103 is Asp, or Ser;

Xaa at position 104 is Trp, Val, Cys, Tyr, Thr, Met, Pro,

Leu, Gln, Lys, Ala, Phe, or Gly;

Xaa at position 105 is Asn, Pro, Ala, Phe, Ser, Trp, Gln, Tyr, Leu, Lys, Ile, or His;

Xaa at position 106 is Glu, Ser, Ala, Lys, Thr, Ile, Gly, or Pro;

Xaa at position 108 is Arg, Asp, Leu, Thr, Ile, or Pro;

Xaa at position 109 is Arg, Thr, Pro, Glu, Tyr, Leu, Ser, or Gly.

9.A composition of 8, wherein said human interleukin-3 mutant polypeptide is of the Formula:

```
        1               5                  10
(Met)m-Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr
            15                  20
Ser Trp Val Asn Cys Ser Xaa Xaa Xaa Asp Glu Ile Ile
25                  30                  35
Xaa His Leu Lys Xaa Pro Pro Xaa Pro Xaa Leu Asp Xaa
        40                  45              50
Xaa Asn Leu Asn Xaa Glu Asp Xaa Asp Ile Leu Xaa Glu
                    55                  60
Xaa Asn Leu Arg Xaa Xaa Asn Leu Xaa Xaa Phe Xaa Xaa
    65                  70              75
Ala Xaa Lys Xaa Leu Xaa Asn Ala Ser Xaa Ile Glu Xaa
            80                  85
Ile Leu Xaa Asn Leu Xaa Pro Cys Xaa Pro Xaa Xaa Thr
90                  95                  100
Ala Xaa Pro Xaa Arg Xaa Pro Ile Xaa Ile Xaa Xaa Gly
        105                 110                 115
Asp Trp Xaa Glu Phe Arg Xaa Lys Leu Xaa Phe Tyr Leu
                    120                 125
Xaa Xaa Leu Glu Xaa Ala Gln Xaa Gln Gln Thr Thr Leu
    130
Ser Leu Ala Ile Phe [SEQ ID NO:7]
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wherein m is 0 or 1; Xaa at position 18 is Asn or Ile; Xaa at position 19 is Met, Ala or Ile; Xaa at position 20 is Ile, Pro or Ile; Xaa at position 23 is Ile, Ala or Leu; Xaa at position 25 is Thr or His; Xaa at position 29 is Gln, Arg, Val or Ile; Xaa at position 32 is Leu, Ala, Asn or Arg; Xaa at position 34 is Leu or Ser; Xaa at

position 37 is Phe, Pro, or Ser; Xaa at position 38 is Asn or Ala; Xaa at position 42 is Gly, Ala, Ser, Asp or Asn; Xaa at position 45 is Gln, Val, or Met; Xaa at position 46 is Asp or Ser; Xaa at position 49 is Met, Ile, Leu or Asp; Xaa at position 50 is Glu or Asp; Xaa at position 51 is Asn Arg or Ser; Xaa at position 55 is Arg, Leu, or Thr; Xaa at position 56 is Pro or Ser; Xaa at position 59 is Glu or Leu; Xaa at position 60 is Ala or Ser; Xaa at position 62 is Asn, Val or Pro; Xaa at position 63 is Arg or His; Xaa at position 65 is Val or Ser; Xaa at position 67 is Ser, Asn, His or Gln; Xaa at position 69 is Gln or Glu; Xaa at position 73 is Ala or Gly; Xaa at position 76 is Ser, Ala or Pro; Xaa at position 79 is Lys, Arg or Ser; Xaa at position 82 is Leu, Glu, Val or Trp; Xaa at position 85 is Leu or Val; Xaa at position 87 is Leu, Ser, Tyr; Xaa at position 88 is Ala or Trp; Xaa at position 91 is Ala or Pro; Xaa at position 93 is Pro or Ser; Xaa at position 95 is His or Thr; Xaa at position 98 is His, Ile, or Thr; Xaa at position 100 is Lys or Arg; Xaa at position 101 is Asp, Ala or Met; Xaa at position 105 is Asn or Glu; Xaa at position 109 is Arg, Glu or Leu; Xaa at position 112 is Thr or Gln; Xaa at position 116 is Lys, Val, Trp or Ser; Xaa at position 117 is Thr or Ser; Xaa at position 120 is Asn, Gln, or His; Xaa at position 123 is Ala or Glu; with the proviso that from four to forty-four of the amino acids designated by Xaa are different from the corresponding amino acids of native human interleukin-3.

10. The composition of 9, wherein said human interleukin-3 mutant polypeptide is of the Formula:

1 5 10
$(Met_m-Ala_n)_p$-Asn Cys Ser Xaa Xaa Xaa Asp Glu Xaa
Ile
15 20
Xaa His Leu Lys Xaa Pro Pro Xaa Pro Xaa Leu Asp Xaa
25 30 35
Xaa Asn Leu Asn Xaa Glu Asp Xaa Xaa Ile Leu Xaa Glu
40 45
Xaa Asn Leu Arg Xaa Xaa Asn Leu Xaa Xaa Phe Xaa Xaa
50 55 60
Ala Xaa Lys Xaa Leu Xaa Asn Ala Ser Xaa Ile Glu Xaa
65 70 75
Ile Leu Xaa Asn Xaa Xaa Pro Cys Xaa Pro Xaa Ala Thr
80 85
Ala Xaa Pro Xaa Arg Xaa Pro Ile Xaa Ile Xaa Xaa Gly
90 95 100
Asp Trp Xaa Glu Phe Arg Xaa Lys Leu Xaa Phe Tyr Leu
105 110
Xaa Xaa Leu Glu Xaa Ala Gln Xaa Gln Gln
[SEQ ID NO:8]

wherein m is 0 or 1; n is 0 or 1; p is 0 or 1; Xaa at position 4 is Asn or Ile; Xaa at position 5 is Met, Ala or Ile: Xaa at position 6 is Ile, Pro or Leu; Xaa at position 9 is Ile, Ala or Leu; Xaa at position 11 is Thr or His; Xaa at position 15 is Gln, Arg, Val or Ile; Xaa at position 18 is Leu, Ala, Asn or Arg; Xaa at position 20 is Leu or Ser; Xaa at position 23 is Phe, Pro, or Ser; Xaa at position 24 is Asn or Ala; Xaa at position 28 is Gly, Ala, Ser, Asp or Asn; Xaa at position 31 is Gln, Val, or Met; Xaa at position 32 is Asp or Ser; Xaa at position 35 is Met, Ile or Asp; Xaa at position 36 is Glu or Asp; Xaa at position 37 is Asn, Arg or Ser; Xaa at position 41 is Arg, Leu, or Thr; Xaa at position 42 is Pro or Ser;

Xaa at position 45 is Glu or Leu; Xaa at position 46 is Ala or Ser; Xaa at position 48 is Asn, Val or Pro; Xaa at position 49 is Arg or His; Xaa at position 51 is Val or Ser; Xaa at position 53 is Ser, Asn, His or Gln; Xaa at position 55 is Gln or Glu; Xaa at position 59 is Ala or Gly; Xaa at position 62 is Ser, Ala or Pro; Xaa at position 65 is Lys, Arg or Ser; Xaa at position 67 is Leu, Glu, or Val; Xaa at position 68 is Leu, Glu, Val or Trp; Xaa at position 71 is Leu or Val; Xaa at position 73 is Leu, Ser or Tyr; Xaa at position 74 is Ala or Trp; Xaa at position 77 is Ala or Pro; Xaa at position 79 is Pro or Ser; Xaa at position 81 is His or Thr; Xaa at position 84 is His, Ile, or Thr; Xaa at position 86 is Lys or Arg; Xaa at position 87 is Asp, Ala or Met; Xaa at position 91 is Asn or Glu; Xaa at position 95 is Arg, Glu, Leu; Xaa at position 98 Thr or Gln; Xaa at position 102 is Lys, Val, Trp or Ser; Xaa at position 103 is Thr or Ser; Xaa at position 106 is Asn, Gln, or His; Xaa at position 109 is Ala or Glu; with the proviso that from four to forty-four of the amino acids designated by Xaa are different from the corresponding amino acids of native (15-125)human interleukin-3.

11. The composition of 10, wherein said human interleukin-3 mutant polypeptide is of the Formula:

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile

His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala
Gln Ala Gln Gln [SEQ ID NO:9];

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His
His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro
Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe
Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala
Gln Ala Gln Gln [SEQ ID NO:10];

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His
His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp Ser
Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe
Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala
Gln Ala Gln Gln [SEQ ID NO:11];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr
His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe
Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met
Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala Phe
Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala
Gln Ala Gln Gln [SEQ ID NO:12];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr
His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe
Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met
Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe
Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala
Gln Ala Gln Gln [SEQ ID NO:13];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr
His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe
Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met
Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe
Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Ala
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala
Gln Ala Gln Gln [SEQ ID NO:14];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr
His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe
Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe
Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly
Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu
Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile
Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Arg
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala
Gln Ala Gln Gln [SEQ ID NO:15];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr
His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe
Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe

Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly
Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu
Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile
Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Arg
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala
Gln Ala Gln Gln [SEQ ID NO:16];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr
His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe
Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe
Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Glu
Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala
Gln Glu Gln Gln [SEQ ID NO:17];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr
His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe
Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe
Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Glu
Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala
Gln Glu Gln Gln [SEQ ID NO:18];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr
His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe
Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met
Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe
Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly
Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys Leu
Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile
Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu

Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln [SEQ ID NO:19];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln [SEQ ID NO:20];

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln Gln [SEQ ID NO:21];

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln [SEQ ID NO:22];

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His

His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp Pro
Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met
Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe
Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Ala
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala
Gln Ala Gln Gln [SEQ ID NO:23];

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His
His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp Ser
Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu Met
Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala Phe
Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala
Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys Leu
Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro Ile
His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg
Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala
Gln Ala Gln Gln [SEQ ID NO:24];

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile
Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp
Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu
Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:25];

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile
Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp
Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu
Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser

Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:26];

Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile
Thr His Leu Lys Gln Pro Pro Leu Pro Leu Leu Asp
Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile Leu
Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His
Ala Gln Glu Gln Gln [SEQ ID NO:27];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys
Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro
Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn
Ala Gln Ala Gln Gln [SEQ ID NO:28];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu
Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser
Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys
Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro
Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn

Ala Gln Ala Gln Gln [SEQ ID NO:29];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp
Ser Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Ala Ile Glu Ser Ile Leu Lys Asn Leu Leu Pro Cys
Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His Pro
Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn
Ala Gln Ala Gln Gln [SEQ ID NO:30];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:31];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu
Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:32];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp

Ser Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:33];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:34];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp
Ser Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:35];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu
Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys

Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His
Ala Gln Glu Gln Gln [SEQ ID NO:36];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Val Pro Pro Ala Pro Leu Leu Asp
Ser Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His
Ala Gln Glu Gln Gln [SEQ ID NO:37];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu
Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:38];

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Val Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His
Ala Gln Glu Gln Gln [SEQ ID NO:39].

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu
Met Asp Arg Asn Leu Arg Leu Ser Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:40]

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ala Ile
His His Leu Lys Arg Pro Pro Ala Pro Ser Leu Asp
Pro Asn Asn Leu Asn Asp Glu Asp Met Ser Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:41]

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp
Pro Asn Asn Leu Asn Asp Glu Asp Met Ser Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:42]

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu

Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:43]

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp
Pro Asn Asn Leu Asn Asp Glu Asp Val Ser Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:44]

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp
Pro Asn Asn Leu Asn Asp Glu Asp Met Ser Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:45]

Met Ala Tyr Pro Glu Thr Asp Tyr Lys Asp Asp Asp
Asp Lys Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Ala Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu
Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:46]

Met Ala Tyr Pro Glu Thr Asp Tyr Lys Asp Asp Asp
Asp Lys Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu
Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:47] and

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Leu Ile
His His Leu Lys Ile Pro Pro Asn Pro Ser Leu Asp
Ser Ala Asn Leu Asn Ser Glu Asp Val Ser Ile Leu
Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:48].

12. The composition of claim 11, wherein said human interleukin-3 mutant polypeptide is of the Formula:

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile
His His Leu Lys Arg Pro Pro Asn Pro Leu Leu Asp
Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu

Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser
Gly Ile Glu Ala Ile Leu Arg Asn Leu Gln Pro Cys
Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln
Ala Gln Glu Gln Gln [SEQ ID NO:32].

Also included in the present invention is a method of increasing multi-lineage hematopoietic cell production in a mammal in need thereof comprising administering a pharmaceutically effective amount of a human interleukin-3 mutant polypeptide as disclosed above with CSF preferably G-CSF or GM-CSF more preferably G-CSF simultaneously as a composition or one after the other.

Materials and methods for IL-3 variant Expression in E. coli

Unless noted otherwise, all specialty chemicals were obtained from Sigma Co., (St. Louis, MO). Restriction endonucleases, T4 poly-nucleotides kinase, E. coli DNA polymerase I large fragment (Klenow) and T4 DNA ligase were obtained from New England Biolabs (Beverly, Massachusetts).

Escherichia coli strains

Strain JM101: delta (pro lac), supE, thi, F'(traD36, rpoAB, lacI-Q, lacZdeltaM15) (Messing, 1979). This strain can be obtained from the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, accession number 33876. MON105 (W3110 rpoH358) is a derivative of W3110 (Bachmann, 1972) and has been assigned ATCC accession number 55204. Strain GM48: dam-3, dcm-6, gal, ara, lac, thr, leu, tonA, tsx (Marinus, 1973) was used to

make plasmid DNA that is not methylated at the sequence GATC.

Genes and plasmids

The gene used for hIL-3 production in E. coli was obtained from British Biotechnology Incorporated, Cambridge, England, catalogue number BBG14. This gene is carried on a pUC based plasmid designated pP0518. Many other human CSF genes can be obtained from R&D Systems, Inc. (Minn, MN) including IL-1 alpha, IL-1 beta, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, G-CSF, GM-CSF and LIF.

The plasmids used for production of hIL-3 in E. coli contain genetic elements whose use has been described (Olins et al., 1988; Olins and Rangwala, 1990). The replicon used is that of pBR327 (Covarrubias, et al., 1981) which is maintained at a copy number of about 100 in the cell (Soberon et al., 1980). A gene encoding the beta-lactamase protein is present on the plasmids. This protein confers ampicillin resistance on the cell. This resistance serves as a selectable phenotype for the presence of the plasmid in the cell.

For cytoplasmic expression vectors the transcription promoter is derived from the recA gene of E. coli (Sancar et al., 1980). This promoter, designated precA, includes the RNA polymerase binding site and the lexA repressor binding site (the operator). This segment of DNA provides high level transcription that is regulated even when the recA promoter is on a plasmid with the pBR327 origin of replication (Olins et al., 1988) incorporated herein by reference.

The ribosome binding site used is that from gene 10 of phage T7 (Olins et al., 1988). This is encoded in a 100 base pair (bp) fragment placed adjacent to precA. In the plasmids used herein, the

recognition sequence for the enzyme NcoI (CCATGG) follows the g10-L. It is at this NcoI site that the hIL-3 genes were joined to the plasmid. It is expected that the nucleotide sequence at this junction will be recognized in mRNA as a functional start site for translation (Olins et al., 1988). The hIL-3 genes used were engineered to have a HindIII recognition site (AAGCTT) downstream from the coding sequence of the gene. At this HindIII site is a 514 base pair RsaI fragment containing the origin of replication of the single stranded phage f1 (Dente et al., 1983; Olins, et al., 1990) both incorporated herein by reference. A plasmid containing these elements is pMON2341. Another plasmid containing these elements is pMON5847 which has been deposited at the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852 under the accession number ATCC 68912.

In secretion expression plasmids the transcription promoter is derived from the *ara B, A,* and *D* genes of E.coli (Greenfield et al., 1978). This promoter is designated p*Ara*BAD and is contained on a 323 base pair *SacII, BglII* restriction fragment. The *LamB* secretion leader (Wong et al., 1988, Clement et al., 1981) is fused to the N-terminus of the hIL-3 gene at the recognition sequence for the enzyme *NcoI* (5'CCATGG3'). The hIL-3 genes used were engineered to have a *HindIII* recognition site (5'AAGCTT3') following the coding sequence of the gene.

Recombinant DNA methods

Synthetic gene assembly

The hIL-3 variant genes and other CSF genes can be constructed by the assembly of synthetic oligonucleotides. Synthetic oligonucleotides were designed so that they would anneal in complementary

pairs, with protruding single stranded ends, and when the pairs were properly assembled would result in a DNA sequence that encoded a portion of the desired gene. Amino acid substitutions in the hIL-3 gene were made by designing the oligonucleotides to encode the desired substitutions. The complementary oligonucleotides were annealed at concentration of 1 picomole per microliter in ligation buffer plus 50mM NaCl. The samples were heated in a 100 ml beaker of boiling water and permitted to cool slowly to room temperature. One picomole of each of the annealed pairs of oligonucleotides were ligated with approximately 0.2 picomoles of plasmid DNA, digested with the appropriate restriction enzymes, in ligation buffer (25 mM Tris pH 8.0, 10 mM $MgCl_2$, 10 mM dithiothreitol, 1 mM ATP, 2mM spermidine) with T4 DNA ligase obtained from New England Biolabs (Beverly, Massachusetts) in a total volume of 20 μl at room temperature overnight.

Polymerase Chain Reaction

Polymerase Chain Reaction (hereafter referred to as PCR) techniques (Saiki, 1985) used the reagent kit and thermal cycler from Perkin-Elmer Cetus (Norwalk, CT.). PCR is based on a thermostable DNA polymerase from Thermus aquaticus. The PCR technique is a DNA amplification method that mimics the natural DNA replication process in that the number of DNA molecules doubles after each cycle, in a way similar to in vivo replication. The DNA polymerase mediated extension is in a 5' to 3' direction. The term "primer" as used herein refers to an oligonucleotide sequence that provides an end to which the DNA polymerase can add nucleotides that were complementary to a nucleotide sequence. The latter nucleotide sequence is referred to as the "template", to which the primers were annealed. The amplified PCR product is defined as the region comprised between the 5' ends of the extension primers.

Since the primers have defined sequences, the product will have discrete ends, corresponding to the primer sequences. The primer extension reaction is carried out using 20 picomoles (pmoles) of each of the oligonucleotides and 1 picogram of template plasmid DNA for 35 cycles (1 cycle is defined as 94 degrees C for one minute, 50 degrees C for two minutes and 72 degrees for three minutes.). The reaction mixture was extracted with an equal volume of phenol/chloroform (50% phenol and 50% chloroform, volume to volume) to remove proteins. The aqueous phase, containing the amplified DNA, and solvent phase were separated by centrifugation for 5 minutes in a microcentrifuge (Model 5414 Eppendorf Inc, Fremont CA.). To precipitate the amplified DNA the aqueous phase was removed and transferred to a fresh tube to which was added 1/10 volume of 3M NaOAc (pH 5.2) and 2.5 volumes of ethanol (100% stored at minus 20 degrees C). The solution was mixed and placed on dry ice for 20 minutes. The DNA was pelleted by centrifugation for 10 minutes in a microcentrifuge and the solution was removed from the pellet. The DNA pellet was washed with 70% ethanol, ethanol removed and dried in a speedvac concentrator (Savant, Farmingdale, New York). The pellet was resuspended in 25 microliters of TE (20mM Tris-HCl pH 7.9, 1mM EDTA). Alternatively the DNA was precipitated by adding equal volume of 4M NH_4OAc and one volume of isopropanol [Treco et al., (1988)]. The solution was mixed and incubated at room temperature for 10 minutes and centrifuged. These conditions selectively precipitate DNA fragments larger than ~ 20 bases and were used to remove oligonucleotide primers. One quarter of the reaction was digested with restriction enzymes [Higuchi, (1989)] an on completion heated to 70 degrees C to inactivate the enzymes.

Recovery of recombinant plasmids from ligation mixes

E. coli JM101 cells were made competent to take up DNA. Typically, 20 to 100 ml of cells were grown in LB medium to a density of approximately 150 Klett units and then collected by centrifugation. The cells were resuspended in one half culture volume of 50 mM $CaCl_2$ and held at 4°C for one hour. The cells were again collected by centrifugation and resuspended in one tenth culture volume of 50 mM $CaCl_2$. DNA was added to a 150 microliter volume of these cells, and the samples were held at 4°C for 30 minutes. The samples were shifted to 42°C for one minute, one milliliter of LB was added, and the samples were shaken at 37°C for one hour. Cells from these samples were spread on plates containing ampicillin to select for transformants. The plates were incubated overnight at 37°C. Single colonies were picked, grown in LB supplemented with ampicillin overnight at 37°C with shaking. From these cultures DNA was isolated for restriction analysis.

Culture medium

LB medium (Maniatis et al., 1982) was used for growth of cells for DNA isolation. M9 minimal medium supplemented with 1.0% casamino acids, acid hydrolyzed casein, Difco (Detroit, Michigan) was used for cultures in which recombinant IL-3 variant was produced. The ingredients in the M9 medium were as follows: 3g/liter KH_2PO_4, 6g/l Na_2HPO_4, 0.5 g/l NaCl, 1 g/l NH_4Cl, 1.2 mM $MgSO_4$, 0.025 mM $CaCl_2$, 0.2% glucose (0.2% glycerol with the AraBAD promoter), 1% casamino acids, 0.1 ml/l trace minerals (per liter 108 g $FeCl_3 \cdot 6H_2O$, 4.0 g $ZnSO_4 \cdot 7H_2O$, 7.0 $CoCl_2 \cdot 2H_2O$, 7.0 g $Na_2MoO_4 \cdot 2H_2O$, 8.0 g $CuSO_4 \cdot 5H_2O$, 2.0 g H_3BO_3, 5.0 g $MnSO_4 \cdot H_2O$, 100 ml concentrated HCl). Bacto agar was used for solid media and ampicillin was added to both liquid and solid LB media at 200 micrograms per milliliter.

Production of IL-3 variants in E. coli with vectors

employing the recA promoter

E. coli strains harboring the plasmids of interest were grown at 37°C in M9 plus casamino acids medium with shaking in a Gyrotory water bath Model G76 from New Brunswick Scientific (Edison, New Jersey). Growth was monitored with a Klett Summerson meter (green 54 filter), Klett Mfg. Co. (New York, New York). At a Klett value of approximately 150, an aliquot of the culture (usually one milliliter) was removed for protein analysis. To the remaining culture, nalidixic acid (10mg/ml) in 0.1 N NaOH was added to a final concentration of 50 μg/ml. The cultures were shaken at 37°C for three to four hours after addition of nalidixic acid. A high degree of aeration was maintained throughout the bacterial growth in order to achieve maximal production of the desired gene product. The cells were examined under a light microscope for the presence of refractile bodies (RBs). One milliliter aliquots of the culture were removed for analysis of protein content.

Extraction, Refolding and Purification of IL-3 Variant Proteins Expressed as Refractile bodies in E. coli

Extraction of refractile bodies (RB's):

For each gram of RB's (and typically one gram is obtained from a 300 ml E. coli culture), 5 ml of a solution containing 6M guanidine hydrochloride (GnHCl), 50 mM 2-N-cyclohexylaminoethanesulfonic acid (CHES) pH 9.5 and 20 mM dithiothreitol (DTT) was added. The RB's were extracted with a Bio-Homogenizer for 15-30 seconds and gently rocked for 2 hours at 5 degrees centigrade (5°C) to allow the protein to completely reduce and denature.

Refolding of the IL-3 muteins

The protein solution was transferred to dialysis

tubing (1000 molecular weight cut-off) and dialyzed against at least 100 volumes of 4M GnHCl - 50 mM CHES pH 8.0. The dialysis was continued overnight at 5°C while gently stirring. Subsequently dialysis was continued against at least 100 volumes of 2M GnHCl - 50 mM CHES pH 8.0 and dialyzed overnight at 5°C while gently stirring.

Purification of the IL-3 muteins

The protein solution was removed from the dialysis tubing and acidified by the addition of 40% acetonitrile (CH_3CN) - 0.2% trifluoroacetic acid (TFA) to a final concentration of 20% CH_3CN - 0.1% TFA. This was centrifuged (16,000 x g for 5 minutes) to clarify and the supernatant was loaded onto a Vydac C-18 reversed phase column (10x250 mm) available from Vydac (Hesperia, California) previously equilibrated in 20% CH_3CN - 0.1% TFA. The column was eluted with a linear gradient (0.2% CH_3CN/minute) between 40 - 50% CH_3CN - 0.1% TFA at a flow rate of 3 ml/minute while collecting 1.5 ml fractions. The fractions were analyzed by polyacrylamide gel electrophoresis (SDS-PAGE) and the appropriate fractions pooled. The pooled material was dried by lyophilization or in a Speed Vac concentrator. The dry powder was reconstituted with 10 mM ammonium bicarbonate pH 7.5, centrifuged (16,000 x g for 5 minutes) to clarify and assayed for protein concentration by the method of Bradford (1976) with bovine serum albumin as the standard. Such protein can be further analyzed by additional techniques such as, SDS-PAGE, electrospray mass spectrometry, reverse phase HPLC, capillary zone electrophoresis, amino acid composition analysis, and ELISA (enzyme-linked immunosorbent assay).

hIL-3 SANDWICH ELISA

The IL-3 variant protein concentrations can be determined using a sandwich ELISA based on an affinity purified polyclonal goat anti-rhIL-3. Microtiter plates (Dynatech Immulon II) were coated with 150 µl goat-anti-rhIL-3 at a concentration of approximately 1 µg/ml in 100 mM NaHCO3, pH 8.2. Plates were incubated overnight at room temperature in a chamber maintaining 100% humidity. Wells were emptied and the remaining reactive sites on the plate were blocked with 200 µl of solution containing 10 mM PBS, 3% BSA and 0.05% Tween 20, pH 7.4 for 1 hour at 37° C and 100% humidity. Wells were emptied and washed 4X with 150 mM NaCl containing 0.05% Tween 20 (wash buffer). Each well then receives 150 µl of dilution buffer (10 mM PBS containing 0.1% BSA, 0.01% Tween 20, pH 7.4), containing rhIL-3 standard, control, sample or dilution buffer alone. A standard curve was prepared with concentrations ranging from 0.125 ng/ml to 5 ng/ml using a stock solution of rhIL-3 (concentration determined by amino acid composition analysis). Plates were incubated 2.5 hours at 37° C and 100% humidity. Wells were emptied and each plate was washed 4X with wash buffer. Each well then received 150 µl of an optimal dilution (as determined in a checkerboard assay format) of goat anti-rhIL-3 conjugated to horseradish peroxidase. Plates were incubated 1.5 hours at 37° C and 100% humidity. Wells were emptied and each plate was washed 4X with wash buffer. Each well then received 150 µl of ABTS substrate solution (Kirkegaard and Perry). Plates were incubated at room temperature until the color of the standard wells containing 5

ng/ml rhIL-3 had developed enough to yield an absorbance between 0.5-1.0 when read at a test wavelength of 410 nm and a reference wavelength of 570 nm on a Dynatech microtiter plate reader. Concentrations of immunoreactive rhIL-3 in unknown samples were calculated from the standard curve using software supplied with the plate reader.

The following examples will illustrate the invention in greater detail although it will be understood that the invention is not limited to these specific examples.

Example 1

Isolation of 1-332 and 1-153 amino acid forms of Meg-CSF

A. Reverse transcriptase reaction Meg-CSF (more recently known as c-mpl ligand) sequence based on Genbank accession #L33410). Human fetal liver A+ RNA was obtained from Clontech (Palo Alto, CA). The first strand cDNA reactions were carried out using a cDNA Cycle™ Kit obtained from Invitrogen (San Diego, CA).

B. Polymerase chain reactions

Following the reverse transcriptase (RT) reaction, the 1-332 c-mpl ligand was amplified via PCR using the oligonucleotide primers c-mplBglII [SEQ ID NO:50] and c-mplEcoRI [SEQ ID NO:51]. Following the RT reaction, the 1-153 c-mpl ligand was amplified using the oligonucleotide primers c-mplNcoI [SEQ ID NO:52] and c-mplHindIII [SEQ ID NO:53].

Example 2

BHK expression vector for full length c-mpl ligand

The full length c-mpl ligand PCR product is digested with BglII and EcoRI restriction enzymes for transfer to a mammalian expression vector. The expression vector, pMON3976, is digested with BamHI and EcoRI, which allows it to accept the BglII-EcoRI PCR fragments. pMON3976 is a derivative of pMON3359 which is a pUC18-based vector containing a mammalian expression cassette. The cassette, which includes a herpes simplex viral promoter IE110 (-800 to +120) and a SV40 late poly-adenylation (poly-A) signal, was subcloned into the pUC18 polylinker [Hippenmeyer et al., (1993)]. The original EcoRI site 5' to the promoter was removed and a new EcoRI site added 3' to the BamHI site. These unique restriction enzyme sites are located between the promoter and poly-A signal to facilitate subcloning DNA fragments as BamHI-EcoRI or BglII-EcoRI fragments in a 5' to 3' direction for transcription and translation. The resulting plasmid encodes the polypeptide with the following amino acid sequence:

Met Glu Leu Thr Glu Leu Leu Leu Val Val Met Leu Leu Leu
Thr Ala Arg Leu Thr Leu Ser Ser Pro Ala Pro Pro Ala Cys
Asp Leu Arg Val Leu Ser Lys Leu Leu Arg Asp Ser His Val
Leu His Ser Arg Leu Ser Gln Cys Pro Glu Val His Pro Leu
Pro Thr Pro Val Leu Leu Pro Ala Val Asp Phe Ser Leu Gly
Glu Trp Lys Thr Gln Met Glu Glu Thr Lys Ala Gln Asp Ile
Leu Gly Ala Val Thr Leu Leu Leu Glu Gly Val Met Ala Ala
Arg Gly Gln Leu Gly Pro Thr Cys Leu Ser Ser Leu Leu Gly
Gln Leu Ser Gly Gln Val Arg Leu Leu Leu Gly Ala Leu Gln
Ser Leu Leu Gly Thr Gln Leu Pro Pro Gln Gly Arg Thr Thr
Ala His Lys Asp Pro Asn Ala Ile Phe Leu Ser Phe Gln His
Leu Leu Arg Gly Lys Val Arg Phe Leu Met Leu Val Gly Gly

Ser Thr Leu Cys Val Arg Arg Ala Pro Pro Thr Thr Ala Val
Pro Ser Arg Thr Ser Leu Val Leu Thr Leu Asn Glu Leu Pro
Asn Arg Thr Ser Gly Leu Leu Glu Thr Asn Phe Thr Ala Ser
Ala Arg Thr Thr Gly Ser Gly Leu Leu Lys Trp Gln Gln Gly
Phe Arg Ala Lys Ile Pro Gly Leu Leu Asn Gln Thr Ser Arg
Ser Leu Asp Gln Ile Pro Gly Tyr Leu Asn Arg Ile His Glu
Leu Leu Asn Gly Thr Arg Gly Leu Phe Pro Gly Pro Ser Arg
Arg Thr Leu Gly Ala Pro Asp Ile Ser Ser Gly Thr Ser Asp
Thr Gly Ser Leu Pro Pro Asn Leu Gln Pro Gly Tyr Ser Pro
Ser Pro Thr His Pro Pro Thr Gly Gln Tyr Thr Leu Phe Pro
Leu Pro Pro Thr Leu Pro Thr Pro Val Val Gln Leu His Pro
Leu Leu Pro Asp Pro Ser Ala Pro Thr Pro Thr Pro Thr Ser
Pro Leu Leu Asn Thr Ser Tyr Thr His Ser Gln Asn Leu Ser
Gln Glu Gly [SEQ ID NO:55]

DNA sequence [SEQ ID NO:54] codes for the foregoing polypeptide.

Example 3

BHK expression vector for 1-153 c-mpl ligand

The 1-153 c-mpl ligand gene product was digested with NcoI and HindIII restriction enzymes for subcloning into pMON3934. pMON3934, a mammalian expression vector, is also derived from pMON3359, but it contains a modified human IL-3 signal peptide sequence in addition to the IE110 promoter and poly-A signal. The signal peptide sequence is flanked by BamHI and NcoI restriction enzyme sites, which facilitates cloning and expression of genes as NcoI-HindIII fragments. The HindIII site is 3' to the NcoI site. The DNA sequence of the signal peptide is shown below (restriction enzyme sites are indicated above). The ATG (methionine) codon within the NcoI site is in-frame with the initiator ATG of the signal peptide (underlined);

BamHI

GGATCCACCATGAGCCGCCTGCCCGTCCTGCTCCTGCTCCAACTCCT

MetSerArgLeuProValLeuLeuLeuLeuGlnLeuLeu

NcoI

GGTCCGCCCCGCCATGG [SEQ ID NO:58]

ValArgProAlaMet [SEQ ID NO:59]

The resulting plasmid was designated pMON26448. The plasmid, pMON26448, encodes the following amino acid sequence:

Met Glu Leu Thr Glu Leu Leu Leu Val Val Met Leu Leu Leu
Thr Ala Arg Leu Thr Leu Ser Ser Pro Ala Pro Pro Ala Cys
Asp Leu Arg Val Leu Ser Lys Leu Leu Arg Asp Ser His Val
Leu His Ser Arg Leu Ser Gln Cys Pro Glu Val His Pro Leu
Pro Thr Pro Val Leu Leu Pro Ala Val Asp Phe Ser Leu Gly
Glu Trp Lys Thr Gln Met Glu Glu Thr Lys Ala Gln Asp Ile
Leu Gly Ala Val Thr Leu Leu Leu Glu Gly Val Met Ala Ala
Arg Gly Gln Leu Gly Pro Thr Cys Leu Ser Ser Leu Leu Gly
Gln Leu Ser Gly Gln Val Arg Leu Leu Leu Gly Ala Leu Gln
Ser Leu Leu Gly Thr Gln Leu Pro Pro Gln Gly Arg Thr Thr
Ala His Lys Asp Pro Asn Ala Ile Phe Leu Ser Phe Gln His
Leu Leu Arg Gly Lys Val Arg Phe Leu Met Leu Val Gly Gly
Ser Thr Leu Cys Val Arg [SEQ ID NO:56]

DNA sequence [SEQ ID NO:54] codes the foregoing amino acid sequence.

For secreted 1-153 c-mpl ligand, the N-terminal sequence should be SerProAla..., like that described elsewhere [de Sauvage et al., (1994)]. For the 1-332 c-mpl ligand, which contains its own secretion signal, it also should be cleaved to leave SerProAla... on the N-terminus. Therefore, the numbering system assumes that SerProAla... are the first three amino acids on either protein.

AML Proliferation Assay for Bioactive Human Interleukin-3

The factor-dependent cell line AML 193 was obtained from the American Type Culture Collection (ATCC, Rockville, MD). This cell line, established from a patient with acute myelogenous leukemia, was a growth factor dependent cell line which displayed enhanced growth in GM/CSF supplemented medium (Lange, B., et al., (1987); Valtieri, M., et al., (1987). The ability of AML 193 cells to proliferate in the presence of human IL-3 has also been documented. (Santoli, D., et al., (1987)). A cell line variant was used, AML 193 1.3, which was adapted for long term growth in IL-3 by washing out the growth factors and starving the cytokine dependent AML 193 cells for growth factors for 24 hours. The cells were then replated at $1x10^5$ cells/well in a 24 well plate in media containing 100 U/ml IL-3. It took approximately 2 months for the cells to grow rapidly in IL-3. These cells were maintained as AML 193 1.3 thereafter by supplementing tissue culture medium (see below) with human IL-3.

AML 193 1.3 cells were washed 6 times in cold Hanks balanced salt solution (HBSS, Gibco, Grand Island, NY) by centrifuging cell suspensions at 250 x g for 10 minutes followed by decantation of supernatant. Pelleted cells were resuspended in HBSS and the procedure was repeated until six wash cycles were completed. Cells washed six times by this procedure were resuspended in tissue culture medium at a density ranging from 2×10^5 to 5×10^5 viable cells/ml. This medium was prepared by supplementing Iscove's modified Dulbecco's Medium (IMDM, Hazelton, Lenexa, KS) with albumin, transferrin, lipids and 2-mercaptoethanol. Bovine albumin (Boehringer-Mannheim, Indianapolis, IN) was added at 500 μg/ml; human transferrin (Boehringer-

Mannheim, Indianapolis, IN) was added at 100 μg/ml; soybean lipid (Boehringer-Mannheim, Indianapolis, IN) was added at 50 μg/ml; and 2-mercaptoethanol (Sigma, St. Louis, MO) was added at 5×10^{-5} M.

Serial dilutions of human interleukin-3 or human interleukin-3 variant protein (hIL-3 mutein) were made in triplicate series in tissue culture medium supplemented as stated above in 96 well Costar 3596 tissue culture plates. Each well contained 50 μl of medium containing interleukin-3 or interleukin-3 variant protein once serial dilutions were completed. Control wells contained tissue culture medium alone (negative control). AML 193 1.3 cell suspensions prepared as above were added to each well by pipetting 50 μl (2.5×10^4 cells) into each well. Tissue culture plates were incubated at 37°C with 5% CO_2 in humidified air for 3 days. On day 3, 0.5 μCi ^{3}H-thymidine (2 Ci/mM, New England Nuclear, Boston, MA) was added in 50 μl of tissue culture medium. Cultures were incubated at 37°C with 5% CO_2 in humidified air for 18-24 hours. Cellular DNA was harvested onto glass filter mats (Pharmacia LKB, Gaithersburg, MD) using a TOMTEC cell harvester (TOMTEC, Orange, CT) which utilized a water wash cycle followed by a 70% ethanol wash cycle. Filter mats were allowed to air dry and then placed into sample bags to which scintillation fluid (Scintiverse II, Fisher Scientific, St. Louis, MO or BetaPlate Scintillation Fluid, Pharmacia LKB, Gaithersburg, MD) was added. Beta emissions of samples from individual tissue culture wells were counted in a LKB Betaplate model 1205 scintillation counter (Pharmacia LKB, Gaithersburg, MD) and data was expressed as counts per minute of ^{3}H-thymidine incorporated into cells from each tissue culture well. Activity of each human interleukin-3 preparation or human interleukin-3 variant preparation was quantitated by measuring cell proliferation (^{3}H-thymidine

incorporation) induced by graded concentrations of interleukin-3 or interleukin-3 variant. Typically, concentration ranges from 0.05 pM - 10^5 pM were quantitated in these assays. Activity was determined by measuring the dose of interleukin-3 or interleukin-3 variant which provides 50% of maximal proliferation [EC_{50} = 0.5 x (maximum average counts per minute of ^3H-thymidine incorporated per well among triplicate cultures of all concentrations of interleukin-3 tested - background proliferation measured by ^3H-thymidine incorporation observed in triplicate cultures lacking interleukin-3]. This EC_{50} value is also equivalent to 1 unit of bioactivity. Every assay was performed with native interleukin-3 as a reference standard so that relative activity levels could be assigned.

Methylcellulose Assay

This assay provides a reasonable approximation of the growth activity of colony stimulating factors to stimulate normal bone marrow cells to produce different types of hematopoietic colonies in vitro (Bradley et al., 1966, Pluznik et al., 1965).

Methods

Approximately 30 ml of fresh, normal, healthy bone marrow aspirate are obtained from individuals. Under sterile conditions samples are diluted 1:5 with a 1X PBS (#14040.059 Life Technologies, Gaithersburg, MD.) solution in a 50 ml conical tube (#25339-50 Corning, Corning MD). Ficoll (Histopaque-1077 Sigma H-8889) is layered under the diluted sample and centrifuged, 300 x g for 30 min. The mononuclear cell band is removed and washed two times in 1X PBS and once with 1% BSA PBS (CellPro Co., Bothel, WA). Mononuclear cells are counted and CD34+ cells are selected using the Ceprate LC (CD34) Kit (CellPro Co., Bothel, WA) column. This

fractionation is performed since all stem and progenitor cells within the bone marrow display CD34 surface antigen. Alternatively whole bone marrow or peripheral blood may be used.

Cultures are set up in triplicate wells with a final volume of 0.1 ml in 48 well tissue culture plates (#3548 CoStar, Cambridge, MA). Culture medium is purchased from Terry Fox Labs. (HCC-4330 medium (Terry Fox Labs, Vancouver, B.C., Canada)). 600-1000 CD34+ cells are added per well. Native IL-3 and IL-3 variants are added to give final concentrations ranging from .001nM-10nM. G-CSF and GM-CSF and C-Kit ligand are added at a final concentration of 0.1nM. Native IL-3 and IL-3 variants are supplied in house. C-Kit Ligand (#255-CS), G-CSF (#214-CS) and GM-CSF (#215-GM) are purchased from R&D Systems (Minneapolis, MN). Cultures are resuspended using an Eppendorf repeater and 0.1 ml is dispensed per well. Control (baseline response) cultures received no colony stimulating factors. Positive control cultures received conditioned media (PHA stimulated human cells:Terry Fox Lab. H2400). Cultures are incubated at 37°C, 5% CO2 in humidified air.

Hematopoietic colonies which are defined as greater than 50 cells are counted on the day of peak response (days 10-11) using a Nikon inverted phase microscope with a 40x objective combination. Groups of cells containing fewer than 50 cells are referred to as clusters. Alternatively colonies can be identified by spreading the colonies on a slide and stained or they can be picked, resuspended and spun onto cytospin slides for staining.

EXAMPLE 4

The synergistic effect of the IL-3 variant, pMON13288, with G-CSF was evaluated in the methylcellulose assay compared to that of native IL-3 with G-CSF. G-CSF was added to each culture at a concentration of 0.1nM. Native IL-3 and the IL-3 variant, pMON13288, were added at final concentrations ranging from 0.001nM to 10nM. Colonies were counted on the day of peak response (days 10-11). pMON13288 activates more progenitor cells than native IL-3 (Figure 2). Native IL-3 plus G-CSF and the IL-3 variant, pMON13288, plus G-CSF resulted in an increase in colony number greater than the additive effect of the individual proteins alone (Figure 2). The synergistic effect of the IL-3 variant, pMON13288, with G-CSF was greater than that of native IL-3 with G-CSF. Hematopoietic colony forming activity of the IL-3 variant, pMON13288, was multi-lineage whereas G-CSF alone activates primarily granulocytic cells at molar equivalent doses. In Figure 2 the concentration of IL-3 is plotted versus the colony counts per 100,000 starting CD34+ cells.

EXAMPLE 5

The synergistic effect of the IL-3 variant, pMON13288, with GM-CSF was evaluated in the methylcellulose assay compared to that of native IL-3 with GM-CSF. GM-CSF was added to each culture at a concentration of 0.1nM. Native IL-3 and the IL-3 variant, pMON13288, were added at final concentrations ranging from 0.001nM to 10nM. Colonies were counted on the day of peak response (days 10-11). pMON13288 activates more progenitor cells than native IL-3 (Figure 3). Native IL-3 plus GM-CSF and the IL-3 variant, pMON13288, plus GM-CSF resulted in an increase in colony number greater than the effect of the individual proteins alone (Figure 3). The synergistic effect of the IL-3 variant, pMON13288, with GM-CSF was greater than that of native IL-3 with GM-

CSF. In Figure 3 the concentration of IL-3 is plotted versus the colony counts per 100,000 starting CD34+ cells.

EXAMPLE 6

Methylcellulose assays for native IL-3, pMON5873, were carried out in methylcellulose, with or without EPO. Although EPO increased the total number of colonies, it didn't appear to increase CFU-GM, which are of more interest. The presence of erythroid colonies also made scoring more subjective, because one must distinguish between multifocal BFU-E vs several closely associated single focus CFU-E. EPO also gave a high background of total colonies, which would tend to obscure the dose dependent response of CFU-GM to other CSFs.

Methylcellulose assays comparing native IL-3 (pMON5873) to the IL-3 variant, pMON13288 were carried out in the presence of stem cell factor (SCF) without EPO. SCF gives no background response in these assays, but appears to increase the dose dependent response of CFU-GM to both native IL-3 (PMON5873) and the IL-3 variant, pMON13288. This result is consistent with reports in the literature of in vitro synergies between IL-3 and SCF (Migliaccio et al., 1992). The IL-3 variant, pMON13288, appears to be more potent in these assays, and gives a greater maximum number of colonies (also larger) than native IL-3 (PMON5873).

Human Cord Blood Hemopoietic Growth Factor Assays

Bone marrow cells are traditionally used for in vitro assays of hematopoietic colony stimulating factor (CSF) activity. However, human bone marrow is not always available, and there is considerable variability between donors. Umbilical cord blood is comparable to

bone marrow as a source of hematopoietic stem cells and progenitors (Broxmeyer et al., 1992; Mayani et al., 1993). In contrast to bone marrow, cord blood is more readily available on a regular basis. There is also a potential to reduce assay variability by pooling cells obtained fresh from several donors, or to create a bank of cryopreserved cells for this purpose. By modifying the culture conditions, and/or analyzing for lineage specific markers, it should be possible to assay specifically for granulocyte / macrophage colonies (CFU-GM), for megakaryocyte CSF activity, or for high proliferative potential colony forming cell (HPP-CFC) activity.

METHODS

Mononuclear cells (MNC) are isolated from cord blood within 24 hrs of collection, using a standard density gradient (1.077g/ml Histopaque). Cord blood MNC have been further enriched for stem cells and progenitors by several procedures, including immunomagnetic selection for CD14-, CD34+ cells; panning for SBA-, CD34+ fraction using coated flasks from Applied Immune Science (Santa Clara, CA); and CD34+ selection using a CellPro (Bothell, WA) avidin column. Either freshly isolated or cryopreserved CD34+ cell enriched fractions are used for the assay. Duplicate cultures for each serial dilution of sample (concentration range from 1pM to 1204pM) are prepared with 1x104 cells in 1ml of .9% methycellulose containing medium without additional growth factors (Methocult H4230 from Stem Cell Technologies, Vancouver, BC.). In some experiments, Methocult H4330 containing erythropoietin (EPO) was used instead of Methocult H4230, or Stem Cell Factor (SCF), 50ng/ml (Biosource International, Camarillo, CA) was added. After culturing for 7-9 days, colonies containing >30 cells are counted. In order to rule out subjective bias in scoring, assays are scored blind.

Analysis of c-mpl ligand proliferative activity

METHODS

1. Bone marrow proliferation assay

a. CD34+ Cell Purification:

Between 15-20 ml bone marrow aspirates were obtained from normal allogeneic marrow donors after informed consent. Cells were diluted 1:3 in phosphate buffered saline (PBS, Gibco-BRL), 30 ml were layered over 15 ml Histopaque-1077 (Sigma) and centrifuged for 30 minutes at 300 RCF. The mononuclear interface layer was collected and washed in PBS. CD34+ cells were enriched from the mononuclear cell preparation using an affinity column per manufacturers instructions (CellPro, Inc, Bothell WA). After enrichment, the purity of CD34+ cells was 70% on average as determined by using flow cytometric analysis using anti CD34 monoclonal antibody conjugated to fluorescein and anti CD38 conjugated to phycoerythrin (Becton Dickinson, San Jose CA).

Cells were resuspended at 40,000 cells/ml in X-Vivo 10 media (Bio-Whittaker, Walkersville, MD) and 1 ml was plated in 12-well tissue culture plates (Costar). The growth factor rhIL-3 was added at 100 ng/ml (pMON5873) was added to some wells. hIL3 variant, pMON13288 was used at 10 ng/ml or 100 ng/ml. Conditioned media from BHK cells transfected with plasmid encoding c-mpl ligand were tested by addition of 100 μl of supernatant added to 1 ml cultures (approximately a 10% dilution). Cells were incubated at 37°C for 8-14 days at 5% CO_2 in a 37°C humidified

incubator.

b. Cell Harvest and Analysis:

At the end of the culture period a total cell count was obtained for each condition. For fluorescence analysis and ploidy determination cells were washed in megakaryocyte buffer (MK buffer, 13.6 mM Sodium Citrate, 1 mM Theophylline, 2.2 μM PGE1, 11 mM Glucose, 3% w/v BSA, in PBS, pH 7.4,) [See Tomer et al., Blood 70, 1987, pp. 1736-42] resuspended in 500 μl of MK buffer containing anti-CD41a FITC antibody (1:200, AMAC, Westbrook, ME) and washed in MK buffer. For DNA analysis cells were permeablized in MK buffer containing 0.5% Tween 20 (Fisher, Fair Lawn NJ) for 20 min. on ice followed by fixation in 0.5% Tween-20 and 1% paraformaldehyde (Fisher Chemical) for 30 minutes followed by incubation in Propidium Iodide (Calbiochem , La Jolla Ca) (50 μg/ml) with RNA-ase (400 U/ml) in 55% v/v MK buffer (200mOsm) for 1-2 hours on ice. Cells were analyzed on a FACScan or Vantage flow cytometer (Becton Dickinson, San Jose, CA). Green fluorescence (CD41a-FITC) was collected along with linear and log signals for red fluorescence (PI) to determine DNA ploidy. All cells were collected to determine the percent of cells that were CD41+. Data analysis was performed using software by LYSIS (Becton Dickinson, San Jose, CA). Percent of cells expressing the CD41 antigen was obtained from flow cytometry analysis(Percent). Absolute (Abs) number of CD41+ cells/ml was calculated by: (Abs)=(Cell Count)*(Percent)/100.

2. Megakaryocyte fibrin clot assay.

CD34+ enriched population were isolated as described above. Cells were suspended at 25,000 cells/ml with/without cytokine(s) in a media consisting of a base Iscoves IMDM media supplemented with 0.3% BSA, 0.4mg/ml apo-transferrin, 6.67μM $FeCl_2$, 25μg/ml $CaCl_2$, 25μg/ml L-asparagine, 500μg/ml E-amino-n-caproic acid and Penicillin/Streptomycin. Prior to plating into 35mm plates, thrombin was added (0.25 Units/ml) to initiate clot formation. Cells were incubated at 37°C for 13 days at 5% CO_2 in a 37°C humidified incubator.

At the end of the culture period plates were fixed with Methanol:Acetone (1:3), air dried and stored at -20°C until staining. A peroxidase immunocytochemistry staining procedure was used (Zymed, Histostain-SP. San Francisco, CA) using a cocktail of primary monoclonal antibodies consisting of anti CD41a, CD42 and CD61. Colonies were counted after staining and classified as negative, CFU-MK (small colonies, 1-2 foci and less that approx. 25 cells), BFU-MK (large, multi-foci colonies with > 25 cells) or mixed colonies (mixture of both positive and negative cells).

Example 7

Co-administration of hIL-3 variant, pMON13288 and c-mpl ligand (Meg-CSF) in liquid culture

Co-administration of hIL-3 variant, pMON13288 and c-mpl ligand (Meg-CSF) has a more than additive effect on megakaryocyte expansion than either cytokine alone in the liquid culture assay

CD34+ cells were isolated as described in the methods section. The assay was set up as described in the methods section except that cells were plated at 4000 cells/100μl in a 96-well plate. pMON26448 or a mock transfectant was evaluated by adding 10 μl to each well (10% final). Supernatant from transfected BHK cells were tested +/- hIL3 variant, pMON13288 (10 ng/ml). At day 10 phenotypic analysis was performed by flow cytometry. Supernatant from pMON26448 induced selective expansion of CD41a+ cells. Total cell number increased from the 4000 cells plated to 22,000 at the end of the assay (Table 1). Addition of hIL3 variant, pMON13288 alone increased total cell numbers (19,000 cells at end of assay) with 17% of cells expressing CD41a. Combination of pMON26448 with hIL3 variant, pMON13288 resulted in 56% of cells expressing CD41a. Total cell expansion in the combination assay was more than additive with 86,000 cells/well. Both the increased total cell number and the higher percentage of cells expressing CD41a resulted in an increase in total number CD41+ cells that also was more than additive as compared to either cytokine alone (48,000 vs. 3,320 and 18,480).

Table 1

Cytokine Treatment	Cells/Well	%CD41a Positive	# CD41+ Cells/Well
pMON13288	19,000	17	3,230
pMON26448	22,000	84	18,480

pMON26448 + pMON13288	86,000	56	48,160

Example 8

Co-administration of hIL-3 variant, pMON13288, and c-mpl ligand (Meg-CSF) in liquid culture

The co-administration of hIL-3 variant, pMON13288, and c-mpl ligand (Meg-CSF) has a more than additive effect on megakaryocyte expansion than either cytokine alone in the liquid culture assay

In another experiment CD34+ cells were isolated from Human bone marrow using a CD34 affinity column (Cellpro). Purified CD34+ cells were resuspended in X-Vivo tissue culture media at 40,000 cells/ml. pMON26448 or a mock transfectant (10%) was evaluated with/without hIL3 variant, pMON13288 or native IL3. At day 8 phenotypic analysis was done using flow cytometry. As was seen in the table below (Table 2a-c). IL3, both concentrations of hIL3 variant, pMON13288 and pMON26448 increased total cell number substantially. Combination of cytokines further expanded cell populations. pMON26448 increased the percent of CD41+ cells from 2% in the control group to 35%. IL3 or hIL3 variant, pMON13288 increased the percent of CD41+ cells modestly (from 2% to 5%). Combining pMON26448 with IL3 or hIL3 variant, pMON13288 resulted in a more than additive number of CD41+ cells as compared to the sum of either cytokine alone (Table 2c).

Table 2(a-c)

a. Total Cells/Well

Cytokine treatment	Media	IL-3 (100ng/ml)	pMON13288 (10ng/ml)	pMON13288 (100ng/ml)
Media	30,000	112,000	275,000	150,000
Mock	10,000	153,000	235,000	260,000
pMON26448	135,000	655,000	625,000	500,000

b. %CD41a+

Cytokine treatment	Media	IL-3 (100ng/ml)	pMON13288 (10ng/ml)	pMON13288 (100ng/ml)
Media	2	7	5	5
Mock	2	14	5	9
pMON26448	35	35	28	29

c. Total CD41a+ Cells

Cytokine treatment	Media	IL-3 (100ng/ml)	pMON13288 (10ng/ml)	pMON13288 (100ng/ml)
Media	600	7,840	13,750	7,500
Mock	200	21,420	11,750	23,400
pMON26448	47,250	229,250	175,000	145,000

Example 9

Co-administration of hIL-3 variant, pMON13288, and c-mpl ligand (Meg-CSF) in fibrin clot assay

The co-administration of hIL-3 variant, pMON13288, and c-mpl ligand (Meg-CSF) has a more than additive effect on megakaryocyte than either cytokine alone.

Fibrin clot cultures were set up as described in methods section. pMON26448 is the 1-153 form of

c-mpl ligand (Meg-CSF). Incubation in the presence of hIL3 variant, pMON13288 gave rise to colonies that were predominantly negative for megakaryocyte markers (86/114, (Table 3)) except for number of small CFU-MK colonies (23/114). pMON26448 alone gave rise primarily to CFU-MK colonies (172/175) with only a few number of negative colonies (3/175). Combination of hIL3 variant, pMON13288 and pMON26448 gave rise to a large number of positive colonies (295/414) that were predominantly of the BFU-MK morphology. There were a negative colonies as well (119/414). Total number of positive colonies with co-administration was more than additive than with either cytokine alone.

Table 3.

Colonies/Well					
Cytokine treatment	Negative	CFU-MK	BFU-MK	Mixed	Total Colonies
pMON13288	86	23	0	5	114
pMON26448	3	73	98	1	175
pMON26448 + pMON13288	119	29	244	22	414
Colonies/100,000 plated					
Cytokine treatment	Negative	CFU-MK	BFU-MK	Mixed	Total Colonies
pMON13288	344	92	0	20	456
pMON26448	12	292	392	4	700
pMON26448 + pMON13288	476	116	976	88	1656

IL-3 mediated sulfidoleukotriene release from human mononuclear cells

The following assay was used to measure IL-3 mediated sulfidoleukotriene release from human mononuclear cells.

Heparin-containing human blood was collected and layered onto an equal volume of Ficoll-Paque

(Pharmacia # 17-0840-02) ready to use medium (density 1.077 g/ml.). The Ficoll was warmed to room temperature prior to use and clear 50 ml polystyrene tubes were utilized. The Ficoll gradient was spun at 300 x g for 30 minutes at room temperature using a H1000B rotor in a Sorvall RT6000B refrigerated centrifuge. The band containing the mononuclear cells was carefully removed, the volume adjusted to 50 mls with Dulbecco's phosphate-buffered saline (Gibco Laboratories cat. # 310-4040PK), spun at 400 x g for 10 minutes at 4°C and the supernatant was carefully removed. The cell pellet was washed twice with HA Buffer [20 mM Hepes (Sigma # H-3375), 125 mM NaCl (Fisher # S271-500), 5 mM KCl (Sigma # P-9541), 0.5 mM glucose (Sigma # G-5000),0.025% Human Serum Albumin (Calbiochem # 126654) and spun at 300 x g, 10 min., 4°C. The cells were resuspended in HACM Buffer (HA buffer supplemented with 1 mM CaCl2 (Fisher # C79-500) and 1 mM MgCl2 (Fisher # M-33) at a concentration of 1 x 106 cells/ml and 180 µl were transferred into each well of 96 well tissue culture plates. The cells were allowed to acclimate at 37°C for 15 minutes. The cells were primed by adding 10 µls of a 20 X stock of various concentrations of cytokine to each well (typically 100000, 20000, 4000, 800, 160, 32, 6.4, 1.28, 0 fM IL3). The cells were incubated for 15 minutes at 37°C. Sulfidoleukotriene release was activated by the addition of 10 µls of 20 X (1000 nM) fmet-leu-phe (Calbiochem # 344252) final concentration 50nM FMLP and incubated for 10 minutes at 37°C. The plates were spun at 350 x g at 4°C for 20 minutes. The supernatants were removed and assayed for sulfidoleukotrienes using Cayman's Leukotriene C4 EIA kit (Cat. #420211) according

to manufacturers' directions. Native (15-125)hIL-3 was run as a standard control in each assay.

Further details known to those skilled in the art may be found in T. Maniatis, et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory (1982) and references cited therein, incorporated herein by reference; and in J. Sambrook, et al., Molecular Cloning, A Laboratory Manual, 2nd edition, Cold Spring Harbor Laboratory (1989) and references cited therein, incorporated herein by reference.

Amino acids are shown herein by standard one letter or three letter abbreviations as follows:

Abbreviated Designation		Amino Acid
A	Ala	Alanine
C	Cys	Cysteine
D	Asp	Aspartic acid
E	Glu	Glutamic acid
F	Phe	Phenylalanine
G	Gly	Glycine
H	His	Histidine
I	Ile	Isoleucine
K	Lys	Lysine
L	Leu	Leucine
M	Met	Methionine
N	Asn	Asparagine
P	Pro	Proline
Q	Gln	Glutamine
R	Arg	Arginine
S	Ser	Serine
T	Thr	Threonine
V	Val	Valine
W	Trp	Tryptophan
Y	Tyr	Tyrosine

Additional details may be found in co-pending United States Patent Application Serial number PCT/US93/11197 which is hereby incorporated by reference in its entirety as if written herein.

All references, patents or applications cited herein are incorporated by reference in their entirety as if written herein.

Various other examples will be apparent to the person skilled in the art after reading the present disclosure without departing from the spirit and scope of the invention. It is intended that all such other examples be included within the scope of the appended claims.

TABLE 4

QLIGONUCLEOTIDES

c-mplBglII

CATGGCAAGATCTCCGGCCAGAATGGAGCTGACTGA [SEQ ID NO:50]

c-mplEcoRI

AATAGCTGAATTCTTACCCTTCCTGAGACAGATT [SEQ ID NO:51]

c-mplNcoI

ACGTCCATGGCNTCNCCNGCNCCNCCTGCTTGTGACCTCCGAGTC

[SEQ ID NO:52]

(where N= G, C, T or A)

c-mplHindIII

TGACAAGCTTACCTGACGCAGAGGGTGGACCCT [SEQ ID NO:53]

TABLE 5
DNA SEQUENCES

1-153 c-mpl ligand

ATGGCGTCTC CGGCGCCGCC TGCTTGTGAC CTCCGAGTCC TCAGTAAACT

GCTTCGTGAC TCCCATGTCC TTCACAGCAG ACTGAGCCAG TGCCCAGAGG
TTCACCCTTT GCCTACACCT GTCCTGCTGC CTGCTGTGGA CTTTAGCTTG
GGAGAATGGA AAACCCAGAT GGAGGAGACC AAGGCACAGG ACATTCTGGG
AGCAGTGACC CTTCTGCTGG AGGGAGTGAT GGCAGCACGG GGACAACTGG
GACCCACTTG CCTCTCATCC CTCCTGGGGC AGCTTTCTGG ACAGGTCCGT
CTCCTCCTTG GGGCCCTGCA GAGCCTCCTT GGAACCCAGC TTCCTCCACA
GGGCAGGACC ACAGCTCACA AGGATCCCAA TGCCATCTTC CTGAGCTTCC
AACACCTGCT CCGAGGAAAG GTGCGTTTCC TGATGCTTGT AGGAGGGTCC
ACCCTCTGCG TCAGG [SEQ ID NO:54]

Full length c-mpl ligand

ATGGAGCTGA CTGAATTGCT CCTCGTGGTC ATGCTTCTCC TAACTGCAAG
GCTAACGCTG TCCAGCCCGG CTCCTCCTGC TTGTGACCTC CGAGTCCTCA
GTAAACTGCT TCGTGACTCC CATGTCCTTC ACAGCAGACT GAGCCAGTGC
CCAGAGGTTC ACCCTTTGCC TACACCTGTC CTGCTGCCTG CTGTGGACTT
TAGCTTGGGA GAATGGAAAA CCCAGATGGA GGAGACCAAG GCACAGGACA
TTCTGGGAGC AGTGACCCTT CTGCTGGAGG GAGTGATGGC AGCACGGGGA
CAACTGGGAC CCACTTGCCT CTCATCCCTC CTGGGGCAGC TTTCTGGACA
GGTCCGTCTC CTCCTTGGGG CCCTGCAGAG CCTCCTTGGA ACCCAGCTTC
CTCCACAGGG CAGGACCACA GCTCACAAGG ATCCCAATGC CATCTTCCTG
AGCTTCCAAC ACCTGCTCCG AGGAAAGGTG CGTTTCCTGA TGCTTGTAGG
AGGGTCCACC CTCTGCGTCA GGCGGGCCCC ACCCACCACA GCTGTCCCCA
GCAGAACCTC TCTAGTCCTC ACACTGAACG AGCTCCCAAA CAGGACTTCT
GGATTGTTGG AGACAAACTT CACTGCCTCA GCCAGAACTA CTGGCTCTGG
GCTTCTGAAG TGGCAGCAGG GATTCAGAGC CAAGATTCCT GGTCTGCTGA
ACCAAACCTC CAGGTCCCTG GACCAAATCC CCGGATACCT GAACAGGATA
CACGAACTCT TGAATGGAAC TCGTGGACTC TTTCCTGGAC CCTCACGCAG
GACCCTAGGA GCCCCGGACA TTTCCTCAGG AACATCAGAC ACAGGCTCCC
TGCCACCCAA CCTCCAGCCT GGATATTCTC CTTCCCCAAC CCATCCTCCT
ACTGGACAGT ATACGCTCTT CCCTCTTCCA CCCACCTTGC CCACCCCTGT
GGTCCAGCTC CACCCCCTGC TTCCTGACCC TTCTGCTCCA ACGCCCACCC
CTACCAGCCC TCTTCTAAAC ACATCCTACA CCCACTCCCA GAATCTGTCT
CAGGAAGGG [SEQ ID NO:57]

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

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(ii) TITLE OF INVENTION: Co-administration of Interleukin-3 Mutant Polypeptides with CSF's for Multi-lineage Hematopoietic Cell Production

(iii) NUMBER OF SEQUENCES: 58

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE: 21-DEC-2001
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 08/446,871
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(B) FILING DATE: 02-FEB-1995

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: US 08/193,373
(B) FILING DATE: 04-FEB-1994

(viii) ATTORNEY/AGENT INFORMATION:
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 133 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Met- may or may not precede the amino acid in position 1"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 17
(D) OTHER INFORMATION: /note= "Xaa at position 17 is Ser, Lys, Gly, Asp, Met, Gln, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 18
(D) OTHER INFORMATION: /note= "Xaa at position 18 is Asn, His, Leu, Ile, Phe, Arg, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 19
(D) OTHER INFORMATION: /note= "Xaa at position 19 is Met, Phe, Ile, Arg, Gly, Ala, or Cys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 20
(D) OTHER INFORMATION: /note= "Xaa at position 20 is Ile, Cys, Gln, Glu, Arg, Pro, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 21
(D) OTHER INFORMATION: /note= "Xaa at position 21 is Asp, Phe, Lys, Arg, Ala, Gly, Glu, Gln, Asn, Thr, Ser, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 22
(D) OTHER INFORMATION: /note= "Xaa at position 22 is Glu, Trp, Pro, Ser, Ala, His, Asp, Asn, Gln, Leu, Val, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 23
(D) OTHER INFORMATION: /note= "Xaa at position 23 is Ile, Val, Ala, Leu, Gly, Trp, Lys, Phe, Ser, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 24
(D) OTHER INFORMATION: /note= "Xaa at position 24 is Ile, Gly, Val, Arg, Ser, Phe, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 25

(D) OTHER INFORMATION: /note= "Xaa at position 25 is Thr, His, Gly, Gln, Arg, Pro, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 26
(D) OTHER INFORMATION: /note= "Xaa at position 26 is His, Thr, Phe, Gly, Arg, Ala, or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 27
(D) OTHER INFORMATION: /note= "Xaa at position 27 is Leu, Gly, Arg, Thr, Ser, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 28
(D) OTHER INFORMATION: /note= "Xaa at position 28 is Lys, Arg, Leu, Gln, Gly, Pro, Val, or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 29
(D) OTHER INFORMATION: /note= "Xaa at position 29 is Gln, Asn, Leu, Pro, Arg, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 30
(D) OTHER INFORMATION: /note= "Xaa at position 30 is Pro, His, Thr, Gly, Asp, Gln, Ser, Leu, or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 31
(D) OTHER INFORMATION: /note= "Xaa at position 31 is Pro, Asp, Gly, Ala, Arg, Leu, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 32
(D) OTHER INFORMATION: /note= "Xaa at position 32 is Leu, Val, Arg, Gln, Asn, Gly, Ala, or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 33
(D) OTHER INFORMATION: /note= "Xaa at position 33 is Pro, Leu, Gln, Ala, Thr, or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 34
(D) OTHER INFORMATION: /note= "Xaa at position 34 is Leu, Val, Gly, Ser, Lys, Glu, Gln, Thr, Arg, Ala, Phe, Ile, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 35
(D) OTHER INFORMATION: /note= "Xaa at position 35 is Leu, Ala, Gly, Asn, Pro, Gln, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 36

(D) OTHER INFORMATION: /note= "Xaa at position 36 is Asp, Leu, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 37
(D) OTHER INFORMATION: /note= "Xaa at position 37 is Phe, Ser, Pro, Trp, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 38
(D) OTHER INFORMATION: /note= "Xaa at position 38 is Asn, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 40
(D) OTHER INFORMATION: /note= "Xaa at position 40 is Leu, Trp, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 41
(D) OTHER INFORMATION: /note= "Xaa at position 41 is Asn, Cys, Arg, Leu, His, Met, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 42
(D) OTHER INFORMATION: /note= "Xaa at position 42 is Gly, Asp, Ser, Cys, Asn, Lys, Thr, Leu, Val, Glu, Phe, Tyr, Ile, Met, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 43
(D) OTHER INFORMATION: /note= "Xaa at position 43 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala, Cys, Gln, Arg, Thr, Gly, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 44
(D) OTHER INFORMATION: /note= "Xaa at position 44 is Asp, Ser, Leu, Arg, Lys, Thr, Met, Trp, Glu, Asn, Gln, Ala, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 45
(D) OTHER INFORMATION: /note= "Xaa at position 45 is Gln, Pro, Phe, Val, Met, Leu, Thr, Lys, Trp, Asp, Asn, Arg, Ser, Ala, Ile, Glu, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 46
(D) OTHER INFORMATION: /note= "Xaa at position 46 is Asp, Phe, Ser, Thr, Cys, Glu, Asn, Gln, Lys, His, Ala, Tyr, Ile, Val, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 47
(D) OTHER INFORMATION: /note= "Xaa at position 47 is Ile, Gly, Val, Ser, Arg, Pro, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 48
(D) OTHER INFORMATION: /note= "Xaa at position 48 is Leu, Ser, Cys, Arg, Ile, His, Phe, Glu, Lys, Thr, Ala, Met, Val, or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 49
(D) OTHER INFORMATION: /note= "Xaa at position 49 is Met, Arg, Ala, Gly, Pro, Asn, His, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 50
(D) OTHER INFORMATION: /note= "Xaa at position 50 is Glu, Leu, Thr, Asp, Tyr, Lys, Asn, Ser, Ala, Ile, Val, His, Phe, Met, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 51
(D) OTHER INFORMATION: /note= "Xaa at position 51 is Asn, Arg, Met, Pro, Ser, Thr, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 52
(D) OTHER INFORMATION: /note= "Xaa at position 52 is Asn, His, Arg, Leu, Gly, Ser, or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 53
(D) OTHER INFORMATION: /note= "Xaa at position 53 is Leu, Thr, Ala, Gly, Glu, Pro, Lys, Ser, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 54
(D) OTHER INFORMATION: /note= "Xaa at position 54 is Arg, Asp, Ile, Ser, Val, Thr, Gln, Asn, Lys, His, Ala, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 55
(D) OTHER INFORMATION: /note= "Xaa at position 55 is Arg, Thr, Val, Ser, Leu, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 56
(D) OTHER INFORMATION: /note= "Xaa at position 56 is Pro, Gly, Cys, Ser, Gln, Glu, Arg, His, Thr, Ala, Tyr, Phe, Leu, Val, or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 57
(D) OTHER INFORMATION: /note= "Xaa at position 57 is Asn or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

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      (B) LOCATION: 58
      (D) OTHER INFORMATION: /note= "Xaa at position 58 is Leu,
          Ser, Asp, Arg, Gln, Val, or Cys"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 59
      (D) OTHER INFORMATION: /note= "Xaa at position 59 is Glu,
          Tyr, His, Leu, Pro, or Arg"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 60
      (D) OTHER INFORMATION: /note= "Xaa at position 60 is Ala,
          Ser, Pro, Tyr, Asn, or Thr"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 61
      (D) OTHER INFORMATION: /note= "Xaa at position 61 is Phe,
          Asn, Glu, Pro, Lys, Arg, or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 62
      (D) OTHER INFORMATION: /note= "Xaa at position 62 is Asn,
          His, Val, Arg, Pro, Thr, Asp, or Ile"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 63
      (D) OTHER INFORMATION: /note= "Xaa at position 63 is Arg,
          Tyr, Trp, Lys, Ser, His, Pro, or Val"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 64
      (D) OTHER INFORMATION: /note= "Xaa at position 64 is Ala,
          Asn, Pro, Ser, or Lys"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 65
      (D) OTHER INFORMATION: /note= "Xaa at position 65 is Val,
          Thr, Pro, His, Leu, Phe, or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 66
      (D) OTHER INFORMATION: /note= "Xaa at position 66 is Lys,
          Ile, Arg, Val, Asn, Glu, or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 67
      (D) OTHER INFORMATION: /note= "Xaa at position 67 is Ser,
          Ala, Phe, Val, Gly, Asn, Ile, Pro, or His"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 68
      (D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu,
          Val, Trp, Ser, Ile, Phe, Thr, or His"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 69
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(D) OTHER INFORMATION: /note= "Xaa at position 69 is Gln, Ala, Pro, Thr, Glu, Arg, Trp, Gly, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 70
(D) OTHER INFORMATION: /note= "Xaa at position 70 is Asn, Leu, Val, Trp, Pro, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 71
(D) OTHER INFORMATION: /note= "Xaa at position 71 is Ala, Met, Leu, Pro, Arg, Glu, Thr, Gln, Trp, or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 72
(D) OTHER INFORMATION: /note= "Xaa at position 72 is Ser, Glu, Met, Ala, His, Asn, Arg, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 73
(D) OTHER INFORMATION: /note= "Xaa at position 73 is Ala, Glu, Asp, Leu, Ser, Gly, Thr, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 74
(D) OTHER INFORMATION: /note= "Xaa at position 74 is Ile, Met, Thr, Pro, Arg, Gly, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 75
(D) OTHER INFORMATION: /note= "Xaa at position 75 is Glu, Lys, Gly, Asp, Pro, Trp, Arg, Ser, Gln, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 76
(D) OTHER INFORMATION: /note= "Xaa at position 76 is Ser, Val, Ala, Asn, Trp, Glu, Pro, Gly, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 77
(D) OTHER INFORMATION: /note= "Xaa at position 77 is Ile, Ser, Arg, Thr, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 78
(D) OTHER INFORMATION: /note= "Xaa at position 78 is Leu, Ala, Ser, Glu, Phe, Gly, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 79
(D) OTHER INFORMATION: /note= "Xaa at position 79 is Lys, Thr, Asn, Met, Arg, Ile, Gly, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

```
      (B) LOCATION: 80
      (D) OTHER INFORMATION: /note= "Xaa at position 80 is Asn,
          Trp, Val, Gly, Thr, Leu, Glu, or Arg"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 81
      (D) OTHER INFORMATION: /note= "Xaa at position 81 is Leu,
          Gln, Gly, Ala, Trp, Arg, Val, or Lys"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 82
      (D) OTHER INFORMATION: /note= "Xaa at position 82 is Leu,
          Gln, Lys, Trp, Arg, Asp, Glu, Asn, His, Thr, Ser, Ala,
          Tyr, Phe, Ile, Met, or Val"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 83
      (D) OTHER INFORMATION: /note= "Xaa at position 83 is Pro,
          Ala, Thr, Trp, Arg, or Met"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 84
      (D) OTHER INFORMATION: /note= "Xaa at position 84 is Cys,
          Glu, Gly, Arg, Met, or Val"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 85
      (D) OTHER INFORMATION: /note= "Xaa at position 85 is Leu,
          Asn, Val, or Gln"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 86
      (D) OTHER INFORMATION: /note= "Xaa at position 86 is Pro,
          Cys, Arg, Ala, or Lys"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 87
      (D) OTHER INFORMATION: /note= "Xaa at position 87 is Leu,
          Ser, Trp, or Gly"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 88
      (D) OTHER INFORMATION: /note= "Xaa at position 88 is Ala,
          Lys, Arg, Val, or Trp"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 89
      (D) OTHER INFORMATION: /note= "Xaa at position 89 is Thr,
          Asp, Cys, Leu, Val, Glu, His, Asn, or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 90
      (D) OTHER INFORMATION: /note= "Xaa at position 90 is Ala,
          Pro, Ser, Thr, Gly, Asp, Ile, or Met"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
```

(B) LOCATION: 91
(D) OTHER INFORMATION: /note= "Xaa at position 91 is Ala, Pro, Ser, Thr, Phe, Leu, Asp, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 92
(D) OTHER INFORMATION: /note= "Xaa at position 92 is Pro, Phe, Arg, Ser, Lys, His, Ala, Gly, Ile, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 93
(D) OTHER INFORMATION: /note= "Xaa at position 93 is Thr, Asp, Ser, Asn, Pro, Ala, Leu, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 94
(D) OTHER INFORMATION: /note= "Xaa at position 94 is Arg, Ile, Ser, Glu, Leu, Val, Gln, Lys, His, Ala, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 95
(D) OTHER INFORMATION: /note= "Xaa at position 95 is His, Gln, Pro, Arg, Val, Leu, Gly, Thr, Asn, Lys, Ser, Ala, Trp, Phe, Ile, or Tyr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 96
(D) OTHER INFORMATION: /note= "Xaa at position 96 is Pro, Lys, Tyr, Gly, Ile, or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 97
(D) OTHER INFORMATION: /note= "Xaa at position 97 is Ile, Val, Lys, Ala, or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 98
(D) OTHER INFORMATION: /note= "Xaa at position 98 is His, Ile, Asn, Leu, Asp, Ala, Thr, Glu, Gln, Ser, Phe, Met, Val, Lys, Arg, Tyr, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 99
(D) OTHER INFORMATION: /note= "Xaa at position 99 is Ile, Leu, Arg, Asp, Val, Pro, Gln, Gly, Ser, Phe, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 100
(D) OTHER INFORMATION: /note= "Xaa at position 100 is Lys, Tyr, Leu, His, Arg, Ile, Ser, Gln, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 101
(D) OTHER INFORMATION: /note= "Xaa at position 101 is Asp, Pro, Met, Lys, His, Thr, Val, Tyr, Glu, Asn, Ser, Ala, Gly, Ile, Leu, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 102
(D) OTHER INFORMATION: /note= "Xaa at position 102 is Gly, Leu, Glu, Lys, Ser, Tyr, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 103
(D) OTHER INFORMATION: /note= "Xaa at position 103 is Asp, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 104
(D) OTHER INFORMATION: /note= "Xaa at position 104 is Trp, Val, Cys, Tyr, Thr, Met, Pro, Leu, Gln, Lys, Ala, Phe, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 105
(D) OTHER INFORMATION: /note= "Xaa at position 105 is Asn, Pro, Ala, Phe, Ser, Trp, Gln, Tyr, Leu, Lys, Ile, Asp, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 106
(D) OTHER INFORMATION: /note= "Xaa at position 106 is Glu, Ser, Ala, Lys, Thr, Ile, Gly, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 108
(D) OTHER INFORMATION: /note= "Xaa at position 108 is Arg, Lys, Asp, Leu, Thr, Ile, Gln, His, Ser, Ala, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 109
(D) OTHER INFORMATION: /note= "Xaa at position 109 is Arg, Thr, Pro, Glu, Tyr, Leu, Ser, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 110
(D) OTHER INFORMATION: /note= "Xaa at position 110 is Lys, Ala, Asn, Thr, Leu, Arg, Gln, His, Glu, Ser, Ala, or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 111
(D) OTHER INFORMATION: /note= "Xaa at position 111 is Leu, Ile, Arg, Asp, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 112
(D) OTHER INFORMATION: /note= "Xaa at position 112 is Thr, Val, Gln, Tyr, Glu, His, Ser, or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 113

(D) OTHER INFORMATION: /note= "Xaa at position 113 is Phe, Ser, Cys, His, Gly, Trp, Tyr, Asp, Lys, Leu, Ile, Val, or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 114
(D) OTHER INFORMATION: /note= "Xaa at position 114 is Tyr, Cys, His, Ser, Trp, Arg, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 115
(D) OTHER INFORMATION: /note= "Xaa at position 115 is Leu, Asn, Val, Pro, Arg, Ala, His, Thr, Trp, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 116
(D) OTHER INFORMATION: /note= "Xaa at position 116 is Lys, Leu, Pro, Thr, Met, Asp, Val, Glu, Arg, Trp, Ser, Asn, His, Ala, Tyr, Phe, Gln, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 117
(D) OTHER INFORMATION: /note= "Xaa at position 117 is Thr, Ser, Asn, Ile, Trp, Lys, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 118
(D) OTHER INFORMATION: /note= "Xaa at position 118 is Leu, Ser, Pro, Ala, Glu, Cys, Asp, or Tyr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 119
(D) OTHER INFORMATION: /note= "Xaa at position 119 is Glu, Ser, Lys, Pro, Leu, Thr, Tyr, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 120
(D) OTHER INFORMATION: /note= "Xaa at position 120 is Asn, Ala, Pro, Leu, His, Val, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 121
(D) OTHER INFORMATION: /note= "Xaa at position 121 is Ala, Ser, Ile, Asn, Pro, Lys, Asp, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 122
(D) OTHER INFORMATION: /note= "Xaa at position 122 is Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, or Cys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 123
(D) OTHER INFORMATION: /note= "Xaa at position 123 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn Cys
1               5                   10                  15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30

Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
    50                  55                  60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65                  70                  75                  80

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
                85                  90                  95

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Phe Xaa Xaa Xaa Xaa Xaa
            100                 105                 110

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gln Gln Thr Thr Leu
        115                 120                 125

Ser Leu Ala Ile Phe
    130
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 133 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Met- may or may not precede the amino acid in position 1"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 17
(D) OTHER INFORMATION: /note= "Xaa at position 17 is Ser, Gly, Asp, Met, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 18
(D) OTHER INFORMATION: /note= "Xaa at position 18 is Asn, His, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 19
(D) OTHER INFORMATION: /note= "Xaa at position 19 is Met or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 21

(D) OTHER INFORMATION: /note="Xaa at position 21 is Asp or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 23
(D) OTHER INFORMATION: /note= "Xaa at position 23 is Ile, Ala, Leu, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 24
(D) OTHER INFORMATION: /note= "Xaa at position 24 is Ile, Val, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 25
(D) OTHER INFORMATION: /note= "Xaa at position 25 is Thr, His, Gln, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 26
(D) OTHER INFORMATION: /note= "Xaa at position 26 is His or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 29
(D) OTHER INFORMATION: /note= "Xaa at position 29 is Gln, Asn, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 30
(D) OTHER INFORMATION: /note= "Xaa at position 30 is Pro, Gly, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 31
(D) OTHER INFORMATION: /note= "Xaa at position 31 is Pro, Asp, Gly, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 32
(D) OTHER INFORMATION: /note= "Xaa at position 32 is Leu, Arg, Gln, Asn, Gly, Ala, or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 33
(D) OTHER INFORMATION: /note= "Xaa at position 33 is Pro or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 34
(D) OTHER INFORMATION: /note= "Xaa at position 34 is Leu, Val, Gly, Ser, Lys, Ala, Arg, Gln, Glu, Ile, Phe, Thr, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 35

(D) OTHER INFORMATION: /note= "Xaa at position 35 is Leu, Ala, Asn, Pro, Gln, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 37
(D) OTHER INFORMATION: /note= "Xaa at position 37 is Phe, Ser, Pro, or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 38
(D) OTHER INFORMATION: /note="Xaa at position 38 is Asn or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 42
(D) OTHER INFORMATION: /note= "Xaa at position 42 is Gly, Asp, Ser, Cys, Ala, Asn, Ile, Leu, Met, Tyr, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 44
(D) OTHER INFORMATON: /note="Xaa at position 44 is Asp or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 45
(D) OTHER INFORMATION: /note= "Xaa at position 45 is Gln, Val, Met, Leu, Thr, Ala, Asn, Glu, Ser, or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 46
(D) OTHER INFORMATION: /note= "Xaa at position 46 is Asp, Phe, Ser, Thr, Ala, Asn, Gln, Glu, His, Ile, Lys, Tyr, Val, or Cys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 50
(D) OTHER INFORMATION: /note= "Xaa at position 50 is Glu, Ala, Asn, Ser, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 51
(D) OTHER INFORMATION: /note= "Xaa at position 51 is Asn, Arg, Met, Pro, Ser, Thr, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 54
(D) OTHER INFORMATON: /note="Xaa at position 54 is Arg or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 55
(D) OTHER INFORMATION: /note= "Xaa at position 55 is Arg, Thr, Val, Leu, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 56

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      (D) OTHER INFORMATION: /note= "Xaa at position 56 is Pro,
          Gly, Ser, Gln, Ala, Arg, Asn, Glu, Leu, Thr, Val,
          or Lys"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 60
      (D) OTHER INFORMATION: /note= "Xaa at position 60 is Ala
          or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 62
      (D) OTHER INFORMATION: /note= "Xaa at position 62 is Asn,
          Pro, Thr, or Ile"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 63
      (D) OTHER INFORMATION: /note= "Xaa at position 63 is Arg
          or Lys"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 64
      (D) OTHER INFORMATION: /note= "Xaa at position 64 is Ala
          or Asn"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 65
      (D) OTHER INFORMATION: /note= "Xaa at position 65 is Val
          or Thr"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 66
      (D) OTHER INFORMATION: /note= "Xaa at position 66 is Lys
          or Arg"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 67
      (D) OTHER INFORMATION: /note= "Xaa at position 67 is Ser
          Phe or His"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 68
      (D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu,
          Ile, Phe, or His"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 69
      (D) OTHER INFORMATION: /note= "Xaa at position 69 is Gln,
          Ala, Pro, Thr, Glu, Arg, or Gly"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 71
      (D) OTHER INFORMATION: /note= "Xaa at position 71 is Ala,
          Pro, or Arg"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 72
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(D) OTHER INFORMATION: /note= "Xaa at position 72 is Ser, Glu, Arg, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 73
(D) OTHER INFORMATION: /note= "Xaa at position 73 is Ala or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 76
(D) OTHER INFORMATION: /note= "Xaa at position 76 is Ser, Val, Ala, Asn, Glu, Pro, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 77
(D) OTHER INFORMATION: /note= "Xaa at position 77 is Ile or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 79
(D) OTHER INFORMATION: /note= "Xaa at position 79 is Lys, Thr, Gly, Asn, Met, Arg, Ile, Gly, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 80
(D) OTHER INFORMATION: /note= "Xaa at position 80 is Asn, Gly, Glu, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 82
(D) OTHER INFORMATION: /note= "Xaa at position 82 is Leu, Gln, Trp, Arg, Asp, Ala, Asn, Glu, His, Ile, Met, Phe, Ser, Thr, Tyr, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 83
(D) OTHER INFORMATION: /note= "Xaa at position 83 is Pro or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 85
(D) OTHER INFORMATION: /note= "Xaa at position 85 is Leu or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 87
(D) OTHER INFORMATION: /note= "Xaa at position 87 is Leu or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 88
(D) OTHER INFORMATION: /note= "Xaa at position 88 is Ala or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 91

(D) OTHER INFORMATION: /note= "Xaa at position 91 is Ala or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 93
(D) OTHER INFORMATION: /note= "Xaa at position 93 is Thr, Asp, Ser, Pro, Ala, Leu, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 95
(D) OTHER INFORMATION: /note= "Xaa at position 95 is His, Pro, Arg, Val, Leu, Gly, Asn, Phe, Ser, or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 96
(D) OTHER INFORMATION: /note= "Xaa at position 96 is Pro or Tyr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 97
(D) OTHER INFORMATION: /note= "Xaa at position 97 is Ile or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 98
(D) OTHER INFORMATION: /note= "Xaa at position 98 is His, Ile, Asn, Leu, Ala, Thr, Arg, Gln, Lys, Met, Ser, Tyr, Val, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 99
(D) OTHER INFORMATION: /note= "Xaa at position 99 is Ile, Leu, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 100
(D) OTHER INFORMATION: /note= "Xaa at position 100 is Lys, Arg, Ile, Gln, Pro, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 101
(D) OTHER INFORMATION: /note= "Xaa at position 101 is Asp, Pro, Met, Lys, Thr, His, Asn, Ile, Leu, or Tyr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 104
(D) OTHER INFORMATION: /note= "Xaa at position 104 is Trp or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 105
(D) OTHER INFORMATION: /note= "Xaa at position 105 is Asn, Pro, Ala, Ser, Trp, Gln, Tyr, Leu, Lys, Ile, Asp, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

```
      (B) LOCATION: 106
      (D) OTHER INFORMATION: /note= "Xaa at position 106 is Glu
          or Gly"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 108
      (D) OTHER INFORMATON: /note="Xaa at position 108 is Arg,
          Ala, or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 109
      (D) OTHER INFORMATION: /note= "Xaa at position 109 is Arg,
          Thr, Glu, Leu, or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 112
      (D) OTHER INFORMATION: /note= "Xaa at position 112 is Thr,
          Val, or Gln"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 114
      (D) OTHER INFORMATION: /note= "Xaa at position 114 is Tyr
          or Trp"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 115
      (D) OTHER INFORMATION: /note= "Xaa at position 115 is Leu
          or Ala"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 116
      (D) OTHER INFORMATION: /note= "Xaa at position 116 is Lys,
          Thr, Val, Trp, Ser, Ala, His, Met, Phe, Tyr, or Ile"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 117
      (D) OTHER INFORMATION: /note= "Xaa at position 117 is Thr
          or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 120
      (D) OTHER INFORMATION: /note= "Xaa at position 120 is Asn,
          Pro, Leu, His, Val, or Gln"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 121
      (D) OTHER INFORMATION: /note= "Xaa at position 121 is Ala,
          Ser, Ile, Asn, Pro, Asp, or Gly"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 122
      (D) OTHER INFORMATION: /note= "Xaa at position 122 is
          Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr,
          or Cys"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
```

(B) LOCATION: 123
(D) OTHER INFORMATION: /note= "Xaa at position 123 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn Cys
1               5                  10                  15

Xaa Xaa Xaa Ile Xaa Glu Xaa Xaa Xaa Xaa Leu Lys Xaa Xaa Xaa Xaa
            20                  25                  30

Xaa Xaa Xaa Asp Xaa Xaa Asn Leu Asn Xaa Glu Xaa Xaa Xaa Ile Leu
        35                  40                  45

Met Xaa Xaa Asn Leu Xaa Xaa Xaa Asn Leu Glu Xaa Phe Xaa Xaa Xaa
    50                  55                  60

Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Ile Glu Xaa Xaa Leu Xaa Xaa
65                  70                  75                  80

Leu Xaa Xaa Cys Xaa Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg Xaa Xaa
                85                  90                  95

Xaa Xaa Xaa Xaa Xaa Gly Asp Xaa Xaa Xaa Phe Xaa Xaa Lys Leu Xaa
            100                 105                 110

Phe Xaa Xaa Xaa Xaa Leu Glu Xaa Xaa Xaa Xaa Gln Gln Thr Thr Leu
        115                 120                 125

Ser Leu Ala Ile Phe
    130
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 133 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Met- may or may not precede the amino acid in position 1"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 17
(D) OTHER INFORMATION: /note= "Xaa at position 17 is Ser, Gly, Asp, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 18
(D) OTHER INFORMATION: /note= "Xaa at position 18 is Asn, His, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 23
(D) OTHER INFORMATION: /note= "Xaa at position 23 is Ile,

Ala, Leu, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 25
(D) OTHER INFORMATION: /note= "Xaa at position 25 is Thr, His, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 26
(D) OTHER INFORMATION: /note= "Xaa at position 26 is His or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 29
(D) OTHER INFORMATION: /note="Xaa at position 29 is Gln or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 30
(D) OTHER INFORMATION: /note= "Xaa at position 30 is Pro or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 32
(D) OTHER INFORMATION: /note= "Xaa at position 32 is Leu, Arg, Asn, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 34
(D) OTHER INFORMATION: /note= "Xaa at position 34 is Leu, Val, Ser, Ala, Arg, Gln, Glu, Ile, Phe, Thr, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 35
(D) OTHER INFORMATION: /note= "Xaa at position 35 is Leu, Ala, Asn, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 38
(D) OTHER INFORMATION: /note= "Xaa at position 38 is Asn or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 42
(D) OTHER INFORMATION: /note= "Xaa at position 42 is Gly, Asp, Ser, Ala, Asn, Ile, Leu, Met, Tyr, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 45
(D) OTHER INFORMATION: /note= "Xaa at position 45 is Gln, Val, Met, Leu, Ala, Asn, Glu, or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 46
(D) OTHER INFORMATION: /note= "Xaa at position 46 is Asp, Phe, Ser, Gln, Glu, His, Val, or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 50
(D) OTHER INFORMATION: /note= "Xaa at position 50 is Glu, Asn, Ser, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 51
(D) OTHER INFORMATION: /note= "Xaa at position 51 is Asn, Arg, Pro, Thr, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 55
(D) OTHER INFORMATION: /note= "Xaa at position 55 is Arg, Leu, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 56
(D) OTHER INFORMATION: /note= "Xaa at position 56 is Pro, Gly, Ser, Ala, Asn, Val, Leu, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 62
(D) OTHER INFORMATION: /note= "Xaa at position 62 is Asn, Pro, or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 64
(D) OTHER INFORMATION: /note= "Xaa at position 64 is Ala or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 65
(D) OTHER INFORMATION: /note= "Xaa at position 65 is Val or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 67
(D) OTHER INFORMATION: /note= "Xaa at position 67 is Ser or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 68
(D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 69
(D) OTHER INFORMATION: /note= "Xaa at position 69 is Gln, Ala, Glu, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 76
(D) OTHER INFORMATION: /note= "Xaa at position 76 is Ser, Val, Asn, Pro, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 77
(D) OTHER INFORMATION: /note= "Xaa at position 77 is Ile or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 79
(D) OTHER INFORMATION: /note= "Xaa at position 79 is Lys, Asn, Met, Arg, Ile, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 80
(D) OTHER INFORMATION: /note= "Xaa at position 80 is Asn, Gly, Glu, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 82
(D) OTHER INFORMATION: /note= "Xaa at position 82 is Leu, Gln, Trp, Arg, Asp, Asn, Glu, His, Met, Phe, Ser, Thr, Tyr, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 87
(D) OTHER INFORMATION: /note= "Xaa at position 87 is Leu or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 88
(D) OTHER INFORMATION: /note= "Xaa at position 88 is Ala or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 91
(D) OTHER INFORMATION: /note= "Xaa at position 91 is Ala or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 93
(D) OTHER INFORMATION: /note= "Xaa at position 93 is Thr, Asp, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 95
(D) OTHER INFORMATION: /note= "Xaa at position 95 is His, Pro, Arg, Val, Gly, Asn, Ser, or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 98
(D) OTHER INFORMATION: /note= "Xaa at position 98 is His, Ile, Asn, Ala, Thr, Gln, Glu, Lys, Met, Ser, Tyr, Val, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 99
(D) OTHER INFORMATION: /note= "Xaa at position 99 is Ile or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 100
(D) OTHER INFORMATION: /note= "Xaa at position 100 is Lys or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 101
(D) OTHER INFORMATION: /note= "Xaa at position 101 is Asp, Pro, Met, Lys, Thr, His, Asn, Ile, Leu, or Tyr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 105
(D) OTHER INFORMATION: /note= "Xaa at position 105 is Asn, Pro, Ser, Ile, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 108
(D) OTHER INFORMATION: /note= "Xaa at position 108 is Arg, Ala, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 109
(D) OTHER INFORMATION: /note= "Xaa at position 109 is Arg, Thr, Glu, Leu, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 112
(D) OTHER INFORMATION: /note= "Xaa at position 112 is Thr or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 116
(D) OTHER INFORMATION: /note= "Xaa at position 116 is Lys, Val, Trp, Ala, His, Phe, Tyr, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 117
(D) OTHER INFORMATION: /note= "Xaa at position 117 is Thr or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 120
(D) OTHER INFORMATION: /note= "Xaa at position 120 is Asn, Pro, Leu, His, Val, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 121
(D) OTHER INFORMATION: /note= "Xaa at position 121 is Ala, Ser, Ile, Pro, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 122
(D) OTHER INFORMATION: /note= "Xaa at position 122 is Gln, Met, Trp, Phe, Pro, His, Ile, or Tyr"

(ix) FEATURE:

(A) NAME/KEY: Modified-site
(B) LOCATION: 123
(D) OTHER INFORMATION: /note= "Xaa at position 123 is Ala, Met, Glu, Ser, or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn Cys
1               5                  10                  15

Xaa Xaa Met Ile Asp Glu Xaa Ile Xaa Xaa Leu Lys Xaa Xaa Pro Xaa
            20                  25                  30

Pro Xaa Xaa Asp Phe Xaa Asn Leu Asn Xaa Glu Asp Xaa Xaa Ile Leu
        35                  40                  45

Met Xaa Xaa Asn Leu Arg Xaa Xaa Asn Leu Glu Ala Phe Xaa Arg Xaa
    50                  55                  60

Xaa Lys Xaa Xaa Xaa Asn Ala Ser Ala Ile Glu Xaa Xaa Leu Xaa Xaa
65                  70                  75                  80

Leu Xaa Pro Cys Leu Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg Xaa Pro
                85                  90                  95

Ile Xaa Xaa Xaa Xaa Gly Asp Trp Xaa Glu Phe Xaa Xaa Lys Leu Xaa
            100                 105                 110

Phe Tyr Leu Xaa Xaa Leu Glu Xaa Xaa Xaa Xaa Gln Gln Thr Thr Leu
        115                 120                 125

Ser Leu Ala Ile Phe
    130
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Met- or Met-Ala- may or may not precede the amino acid in position 1"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 3
(D) OTHER INFORMATION: /note= "Xaa at position 3 is Ser, Lys, Gly, Asp, Met, Gln, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 4
(D) OTHER INFORMATION: /note= "Xaa at position 4 is Asn, His, Leu, Ile, Phe, Arg, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5

```
      (D) OTHER INFORMATION: /note= "Xaa at position 5 is Met,
          Phe, Ile, Arg, Gly, Ala, or Cys"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 6
      (D) OTHER INFORMATION: /note= "Xaa at position 6 is Ile,
          Cys, Gln, Glu, Arg, Pro, or Ala"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 7
      (D) OTHER INFORMATION: /note= "Xaa at position 7 is Asp,
          Phe, Lys, Arg, Ala, Gly, Glu, Gln, Asn, Thr, Ser,
          or Val"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 8
      (D) OTHER INFORMATION: /note= "Xaa at position 8 is Glu,
          Trp, Pro, Ser, Ala, His, Asp, Asn, Gln, Leu, Val,
          or Gly"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 9
      (D) OTHER INFORMATION: /note= "Xaa at position 9 is
          Ile, Val, Ala, Leu, Gly, Trp, Lys, Phe, Leu, Ser
          or Arg"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 10
      (D) OTHER INFORMATION: /note= "Xaa at position 10 is Ile,
          Gly, Val, Arg, Ser, Phe, or Leu"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 11
      (D) OTHER INFORMATION: /note= "Xaa at position 11 is Thr,
          His, Gly, Gln, Arg, Pro, or Ala"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 12
      (D) OTHER INFORMATION: /note= "Xaa at position 12 is His,
          Thr, Phe, Gly, Arg, Ala, or Trp"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 13
      (D) OTHER INFORMATION: /note= "Xaa at position 13 is Leu,
          Gly, Arg, Thr, Ser, or Ala"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 14
      (D) OTHER INFORMATION: /note= "Xaa at position 14 is Lys,
          Arg, Leu, Gln, Gly, Pro, Val, or Trp"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 15
      (D) OTHER INFORMATION: /note= "Xaa at position 15 is Gln,
          Asn, Leu, Pro, Arg, or Val"

(ix) FEATURE:
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      (A) NAME/KEY: Modified-site
      (B) LOCATION: 16
      (D) OTHER INFORMATION: /note= "Xaa at position 16 is Pro,
          His, Thr, Gly, Asp, Gln, Ser, Leu, or Lys"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 17
      (D) OTHER INFORMATION: /note= "Xaa at position 17 is Pro,
          Asp, Gly, Ala, Arg, Leu, or Gln"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 18
      (D) OTHER INFORMATION: /note= "Xaa at position 18 is Leu,
          Val, Arg, Gln, Asn, Gly, Ala, or Glu"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 19
      (D) OTHER INFORMATION: /note= "Xaa at position 19 is Pro,
          Leu, Gln, Ala, Thr, or Glu"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 20
      (D) OTHER INFORMATION: /note= "Xaa at position 20 is Leu,
          Val, Gly, Ser, Lys, Glu, Gln, Thr, Arg, Ala, Phe,
          Ile, or Met"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 21
      (D) OTHER INFORMATION: /note= "Xaa at position 21 is Leu,
          Ala, Gly, Asn, Pro, Gln, or Val"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 22
      (D) OTHER INFORMATION: /note= "Xaa at position 22 is Asp,
          Leu, or Val"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 23
      (D) OTHER INFORMATION: /note= "Xaa at position 23 is Phe,
          Ser, Pro, Trp, or Ile"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 24
      (D) OTHER INFORMATION: /note= "Xaa at position 24 is Asn
          or Ala"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 26
      (D) OTHER INFORMATION: /note= "Xaa at position 26 is Leu,
          Trp, or Arg"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 27
      (D) OTHER INFORMATION: /note= "Xaa at position 27 is Asn,
          Cys, Arg, Leu, His, Met, or Pro"

(ix) FEATURE:
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(A) NAME/KEY: Modified-site
(B) LOCATION: 28
(D) OTHER INFORMATION: /note= "Xaa at position 28 is Gly, Asp, Ser, Cys, Ala, Lys, Asn, Thr, Leu, Val, Glu, Phe, Tyr, Ile, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 29
(D) OTHER INFORMATION: /note= "Xaa at position 29 is Glu, Asn, Tyr, Leu, Phe, Asp, Ala, Cys, Gln, Arg, Thr, Gly, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 30
(D) OTHER INFORMATION: /note= "Xaa at position 30 is Asp, Ser, Leu, Arg, Lys, Thr, Met, Trp, Glu, Asn, Gln, Ala, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 31
(D) OTHER INFORMATION: /note= "Xaa at position 31 is Gln, Pro, Phe, Val, Met, Leu, Thr, Lys, Asp, Asn, Arg, Ser, Ala, Ile, Glu, His, or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 32
(D) OTHER INFORMATION: /note= "Xaa at position 32 is Asp, Phe, Ser, Thr, Cys, Glu, Asn, Gln, Lys, His, Ala, Tyr, Ile, Val, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 33
(D) OTHER INFORMATION: /note= "Xaa at position 33 is Ile, Gly, Val, Ser, Arg, Pro, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 34
(D) OTHER INFORMATION: /note= "Xaa at position 34 is Leu, Ser, Cys, Arg, Ile, His, Phe, Glu, Lys, Thr, Ala, Met, Val, or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 35
(D) OTHER INFORMATION: /note= "Xaa at position 35 is Met, Arg, Ala, Gly, Pro, Asn, His, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 36
(D) OTHER INFORMATION: /note= "Xaa at position 36 is Glu, Leu, Thr, Asp, Tyr, Lys, Asn, Ser, Ala, Ile, Val, His, Phe, Met, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 37
(D) OTHER INFORMATION: /note= "Xaa at position 37 is Asn, Arg, Met, Pro, Ser, Thr, or His"

(ix) FEATURE:

(A) NAME/KEY: Modified-site
(B) LOCATION: 38
(D) OTHER INFORMATION: /note= "Xaa at position 38 is Asn, His, Arg, Leu, Gly, Ser, or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 39
(D) OTHER INFORMATION: /note= "Xaa at position 39 is Leu, Thr, Ala, Gly, Glu, Pro, Lys, Ser, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 40
(D) OTHER INFORMATION: /note= "Xaa at position 40 is Arg, Asp, Ile, Ser, Val, Thr, Gln, Asn, Lys, His, Ala, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 41
(D) OTHER INFORMATION: /note= "Xaa at position 41 is Arg, Thr, Val, Ser, Leu, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 42
(D) OTHER INFORMATION: /note= "Xaa at position 42 is Pro, Gly, Cys, Ser, Gln, Glu, Arg, His, Thr, Ala, Tyr, Phe, Leu, Val, or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 43
(D) OTHER INFORMATION: /note= "Xaa at position 43 is Asn or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 44
(D) OTHER INFORMATION: /note= "Xaa at position 44 is Leu, Ser, Asp, Arg, Gln, Val, or Cys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 45
(D) OTHER INFORMATION: /note= "Xaa at position 45 is Glu, Tyr, His, Leu, Pro, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 46
(D) OTHER INFORMATION: /note= "Xaa at position 46 is Ala, Ser, Pro, Tyr, Asn, or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 47
(D) OTHER INFORMATION: /note= "Xaa at position 47 is Phe, Asn, Glu, Pro, Lys, Arg, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 48
(D) OTHER INFORMATION: /note= "Xaa at position 48 is Asn, His, Val, Arg, Pro, Thr, Asp, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 49
(D) OTHER INFORMATION: /note= "Xaa at position 49 is Arg, Tyr, Trp, Lys, Ser, His, Pro, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 50
(D) OTHER INFORMATION: /note= "Xaa at position 50 is Ala, Asn, Pro, Ser, or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 51
(D) OTHER INFORMATION: /note= "Xaa at position 51 is Val, Thr, Pro, His, Leu, Phe, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 52
(D) OTHER INFORMATION: /note= "Xaa at position 52 is Lys, Ile, Arg, Val, Asn, Glu, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 53
(D) OTHER INFORMATION: /note= "Xaa at position 53 is Ser, Ala, Phe, Val, Gly, Asn, Ile, Pro, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 54
(D) OTHER INFORMATION: /note= "Xaa at position 54 is Leu, Val, Trp, Ser, Ile, Phe, Thr, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 55
(D) OTHER INFORMATION: /note= "Xaa at position 55 is Gln, Ala, Pro, Thr, Glu, Arg, Trp, Gly, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 56
(D) OTHER INFORMATION: /note= "Xaa at position 56 is Asn, Leu, Val, Trp, Pro, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 57
(D) OTHER INFORMATION: /note= "Xaa at position 57 is Ala, Met, Leu, Pro, Arg, Glu, Thr, Gln, Trp, or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 58
(D) OTHER INFORMATION: /note= "Xaa at position 58 is Ser, Glu, Met, Ala, His, Asn, Arg, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 59
(D) OTHER INFORMATION: /note= "Xaa at position 59 is Ala, Glu, Asp, Leu, Ser, Gly, Thr, or Arg"

(ix) FEATURE:

(A) NAME/KEY: Modified-site
(B) LOCATION: 60
(D) OTHER INFORMATION: /note= "Xaa at position 60 is Ile, Met, Thr, Pro, Arg, Gly, Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 61
(D) OTHER INFORMATION: /note= "Xaa at position 61 is Glu, Lys, Gly, Asp, Pro, Trp, Arg, Ser, Gln, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 62
(D) OTHER INFORMATION: /note= "Xaa at position 62 is Ser, Val, Ala, Asn, Trp, Glu, Pro, Gly, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 63
(D) OTHER INFORMATION: /note= "Xaa at position 63 is Ile, Ser, Arg, Thr, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 64
(D) OTHER INFORMATION: /note= "Xaa at position 64 is Leu, Ala, Ser, Glu, Phe, Gly, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 65
(D) OTHER INFORMATION: /note= "Xaa at position 65 is Lys, Thr, Gly, Asn, Met, Arg, Ile, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 66
(D) OTHER INFORMATION: /note= "Xaa at position 66 is Asn, Trp, Val, Gly, Thr, Leu, Glu, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 67
(D) OTHER INFORMATION: /note= "Xaa at position 67 is Leu, Gln, Gly, Ala, Trp, Arg, Val, or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 68
(D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu, Gln, Lys, Trp, Arg, Asp, Glu, Asn, His, Thr, Ser, Ala, Tyr, Phe, Ile, Met, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 69
(D) OTHER INFORMATION: /note= "Xaa at position 69 is Pro, Ala, Thr, Trp, Arg, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 70
(D) OTHER INFORMATION: /note= "Xaa at position 70 is Cys, Glu, Gly, Arg, Met, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 71
(D) OTHER INFORMATION: /note= "Xaa at position 71 is Leu, Asn, Val, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 72
(D) OTHER INFORMATION: /note= "Xaa at position 72 is Pro, Cys, Arg, Ala, or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 73
(D) OTHER INFORMATION: /note= "Xaa at position 73 is Leu, Ser, Trp, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 74
(D) OTHER INFORMATION: /note= "Xaa at position 74 is Ala, Lys, Arg, Val, or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 75
(D) OTHER INFORMATION: /note= "Xaa at position 75 is Thr, Asp, Cys, Leu, Val, Glu, His, Asn, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 76
(D) OTHER INFORMATION: /note= "Xaa at position 76 is Ala, Pro, Ser, Thr, Gly, Asp, Ile, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 77
(D) OTHER INFORMATION: /note= "Xaa at position 77 is Ala, Pro, Ser, Thr, Phe, Leu, Asp, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 78
(D) OTHER INFORMATION: /note= "Xaa at position 78 is Pro, Phe, Arg, Ser, Lys, His, Ala, Gly, Ile, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 79
(D) OTHER INFORMATION: /note= "Xaa at position 79 is Thr, Asp, Ser, Asn, Pro, Ala, Leu, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 80
(D) OTHER INFORMATION: /note= "Xaa at position 80 is Arg, Ile, Ser, Glu, Leu, Val, Gln, Lys, His, Ala, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 81
(D) OTHER INFORMATION: /note= "Xaa at position 81 is His, Gln, Pro, Arg, Val, Leu, Gly, Thr, Asn, Lys, Ser, Ala, Trp, Phe, Ile, or Tyr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 82
(D) OTHER INFORMATION: /note= "Xaa at position 82 is Pro, Lys, Tyr, Gly, Ile, or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 83
(D) OTHER INFORMATION: /note= "Xaa at position 83 is Ile, Val, Lys, Ala, or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 84
(D) OTHER INFORMATION: /note= "Xaa at position 84 is His, Ile, Asn, Leu, Asp, Ala, Thr, Glu, Gln, Ser, Phe, Met, Val, Lys, Arg, Tyr, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 85
(D) OTHER INFORMATION: /note= "Xaa at position 85 is Ile, Leu, Arg, Asp, Val, Pro, Gln, Gly, Ser, Phe, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 86
(D) OTHER INFORMATION: /note= "Xaa at position 86 is Lys, Tyr, Leu, His, Arg, Ile, Ser, Gln, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 87
(D) OTHER INFORMATION: /note= "Xaa at position 87 is Asp, Pro, Met, Lys, His, Thr, Val, Tyr, Glu, Asn, Ser, Ala, Gly, Ile, Leu, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 88
(D) OTHER INFORMATION: /note= "Xaa at position 88 Gly, Leu, Glu, Lys, Ser, Tyr, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 89
(D) OTHER INFORMATION: /note= "Xaa at position 89 is Asp or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 90
(D) OTHER INFORMATION: /note= "Xaa at position 90 is Trp, Val, Cys, Tyr, Thr, Met, Pro, Leu, Gln, Lys, Ala, Phe, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 91
(D) OTHER INFORMATION: /note= "Xaa at position 91 is Asn, Pro, Ala, Phe, Ser, Trp, Gln, Tyr, Leu, Lys, Ile, Asp, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

(B) LOCATION: 92
(D) OTHER INFORMATION: /note= "Xaa at position 92 is Glu, Ser, Ala, Lys, Thr, Ile, Gly, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 94
(D) OTHER INFORMATION: /note= "Xaa at position 94 is Arg, Lys, Asp, Leu, Thr, Ile, Gln, His, Ser, Ala, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 95
(D) OTHER INFORMATION: /note= "Xaa at position 95 is Arg, Thr, Pro, Glu, Tyr, Leu, Ser, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 96
(D) OTHER INFORMATION: /note= "Xaa at position 96 is Lys, Asn, Thr, Leu, Gln, Arg, His, Glu, Ser, Ala, or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 97
(D) OTHER INFORMATION: /note= "Xaa at position 97 is Leu, Ile, Arg, Asp, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 98
(D) OTHER INFORMATION: /note= "Xaa at position 98 is Thr, Val, Gln, Tyr, Glu, His, Ser, or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 99
(D) OTHER INFORMATION: /note= "Xaa at position 99 is Phe, Ser, Cys, His, Gly, Trp, Tyr, Asp, Lys, Leu, Ile, Val, or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 100
(D) OTHER INFORMATION: /note= "Xaa at position 100 is Tyr, Cys, His, Ser, Trp, Arg, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 101
(D) OTHER INFORMATION: /note= "Xaa at position 101 is Leu, Asn, Val, Pro, Arg, Ala, His, Thr, Trp, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 102
(D) OTHER INFORMATION: /note= "Xaa at position 102 is Lys, Leu, Pro, Thr, Met, Asp, Val, Glu, Arg, Trp, Ser, Asn, His, Ala, Tyr, Phe, Gln, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 103
(D) OTHER INFORMATION: /note= "Xaa at position 103 is Thr, Ser, Asn, Ile, Trp, Lys, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 104
(D) OTHER INFORMATION: /note= "Xaa at position 104 is Leu, Ser, Pro, Ala, Glu, Cys, Asp, or Tyr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 105
(D) OTHER INFORMATION: /note= "Xaa at position 105 is Glu, Ser, Lys, Pro, Leu, Thr, Tyr, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 106
(D) OTHER INFORMATION: /note= "Xaa at position 106 is Asn, Ala, Pro, Leu, His, Val or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 107
(D) OTHER INFORMATION: /note= "Xaa at position 107 is Ala, Ser, Ile, Asn, Pro, Lys, Asp, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 108
(D) OTHER INFORMATION: /note= "Xaa at position 108 is Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, or Cys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 109
(D) OTHER INFORMATION: /note= "Xaa at position 109 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Asn Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1               5                   10                  15

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25                  30

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
        35                  40                  45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
    50                  55                  60

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65                  70                  75                  80

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Phe Xaa Xaa Xaa
                85                  90                  95

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Met- or Met-Ala- may or may not precede the amino acid in position 1"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 3
(D) OTHER INFORMATION: /note= "Xaa at position 3 is Ser, Gly, Asp, Met, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 4
(D) OTHER INFORMATION: /note= "Xaa at position 4 is Asn, His, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION: /note= "Xaa at position 5 is Met or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 7
(C) OTHER INFORMATON: /note= "Xaa at position 7 is Asp or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 9
(D) OTHER INFORMATION: /note= "Xaa at position 9 is Ile, Ala, Leu, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 10
(D) OTHER INFORMATION: /note= "Xaa at position 10 is Ile, Val, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 11
(D) OTHER INFORMATION: /note= "Xaa at position 11 is Thr, His, Gln, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 12
(D) OTHER INFORMATION: /note= "Xaa at position 12 is His or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 15
(D) OTHER INFORMATION: /note= "Xaa at position 15 is Gln, Asn, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 16

(D) OTHER INFORMATION: /note= "Xaa at position 16 is Pro, Gly, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 17
(D) OTHER INFORMATION: /note= "Xaa at position 17 is Pro, Asp, Gly, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 18
(D) OTHER INFORMATION: /note= "Xaa at position 18 is Leu, Arg, Gln, Asn, Gly, Ala, or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 19
(D) OTHER INFORMATION: /note= "Xaa at position 19 is Pro or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 20
(D) OTHER INFORMATION: /note= "Xaa at position 20 is Leu, Val, Gly, Ser, Lys, Ala, Arg, Gln, Glu, Ile, Phe, Thr, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 21
(D) OTHER INFORMATION: /note= "Xaa at position 21 is Leu, Ala, Asn, Pro, Gln, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 23
(D) OTHER INFORMATION: /note= "Xaa at position 23 is Phe, Ser, Pro, or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 24
(D) OTHER INFORMATION: /note= "Xaa at position 24 is Asn or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 28
(D) OTHER INFORMATION: /note= "Xaa at position 28 is Gly, Asp, Ser, Cys, Ala, Asn, Ile, Leu, Met, Tyr, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 30
(D) OTHER INFORMATION: /note= "Xaa at position 30 is Asp or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 31
(D) OTHER INFORMATION: /note= "Xaa at position 31 is Gln, Val, Met, Leu, Thr, Ala, Asn, Glu, Ser, or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 32

(D) OTHER INFORMATION: /note= "Xaa at position 32 is Asp, Phe, Ser, Thr, Ala, Asn, Gln, Glu, His, Ile, Lys, Tyr, Val, or Cys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 36
(D) OTHER INFORMATION: /note= "Xaa at position 36 is Glu, Ala, Asn, Ser, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 37
(D) OTHER INFORMATION: /note= "Xaa at position 37 is Asn, Arg, Met, Pro, Ser, Thr, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 40
(D) OTHER INFORMATION: /note= "Xaa at position 40 is Arg or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 41
(D) OTHER INFORMATION: /note= "Xaa at position 41 is Arg, Thr, Val, Leu, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 42
(D) OTHER INFORMATION: /note= "Xaa at position 42 is Pro, Gly, Ser, Gln, Ala, Arg, Asn, Glu, Leu, Thr, Val, or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 46
(D) OTHER INFORMATION: /note= "Xaa at position 46 is Ala or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 48
(D) OTHER INFORMATION: /note= "Xaa at position 48 is Asn, Pro, Thr, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 49
(D) OTHER INFORMATION: /note= "Xaa at position 49 is Arg or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 50
(D) OTHER INFORMATION: /note= "Xaa at position 50 is Ala or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 51
(D) OTHER INFORMATION: /note= "Xaa at position 51 is Val or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

```
      (B) LOCATION: 52
      (D) OTHER INFORMATION: /note= "Xaa at position 52 is Lys
          or Arg"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 53
      (D) OTHER INFORMATION: /note= "Xaa at position 53 is Ser,
          Phe, or His"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 54
      (D) OTHER INFORMATION: /note= "Xaa at position 54 is Leu,
          Ile, Phe, or His"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 55
      (D) OTHER INFORMATION: /note= "Xaa at position 55 is Gln,
          Ala, Pro, Thr, Glu, Arg, or Gly"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 57
      (D) OTHER INFORMATION: /note= "Xaa at position 57 is Ala,
          Pro, or Arg"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 58
      (D) OTHER INFORMATION: /note= "Xaa at position 58 is Ser,
          Glu, Arg, or Asp"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 59
      (D) OTHER INFORMATION: /note= "Xaa at position 59 is Ala
          or Leu"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 62
      (D) OTHER INFORMATION: /note= "Xaa at position 62 is Ser,
          Val, Ala, Asn, Glu, Pro, or Gly"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 63
      (D) OTHER INFORMATION: /note= "Xaa at position 63 is Ile
          or Leu"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 65
      (D) OTHER INFORMATION: /note= "Xaa at position 65 is Lys,
          Thr, Gly, Asn, Met, Arg, Ile, Gly, or Asp"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 66
      (D) OTHER INFORMATION: /note= "Xaa at position 66 is Asn,
          Gly, Glu, or Arg"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 68
```

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      (D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu,
          Gln, Trp, Arg, Asp, Ala, Asn, Glu, His, Ile, Met,
          Phe, Ser, Thr, Tyr, or Val"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 69
      (D) OTHER INFORMATION: /note= "Xaa at position 69 is Pro
          or Thr"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 71
      (D) OTHER INFORMATION: /note= "Xaa at position 71 is Leu
          or Val"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 73
      (D) OTHER INFORMATION: /note= "Xaa at position 73 is Leu
          or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 74
      (D) OTHER INFORMATION: /note= "Xaa at position 74 is Ala
          or Trp"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 77
      (D) OTHER INFORMATION: /note= "Xaa at position 77 is Ala
          or Pro"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 79
      (D) OTHER INFORMATION: /note= "Xaa at position 79 is Thr,
          Asp, Ser, Pro, Ala, Leu, or Arg"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 81
      (D) OTHER INFORMATION: /note= "Xaa at position 81 is His,
          Pro, Arg, Val, Leu, Gly, Asn, Phe, Ser, or Thr"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 82
      (D) OTHER INFORMATION: /note= "Xaa at position 82 is Pro
          or Tyr"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 83
      (D) OTHER INFORMATION: /note= "Xaa at position 83 is Ile
          or Val"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 84
      (D) OTHER INFORMATION: /note= "Xaa at position 84 is His,
          Ile, Asn, Leu, Ala, Thr, Arg, Gln, Lys,
          Met, Ser, Tyr, Val, or Pro"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
```

(B) LOCATION: 85
(D) OTHER INFORMATION: /note= "Xaa at position 85 is Ile, Leu, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 86
(D) OTHER INFORMATION: /note= "Xaa at position 86 is Lys, Arg, Ile, Gln, Pro, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 87
(D) OTHER INFORMATION: /note= "Xaa at position 87 is Asp, Pro, Met, Lys, His, Thr, Asn, Ile, Leu, or Tyr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 90
(D) OTHER INFORMATION: /note= "Xaa at position 90 is Trp or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 91
(D) OTHER INFORMATION: /note="Xaa at position 91 is Asn, Pro, Ala, Ser, Trp, Gln, Tyr, Leu, Lys, Ile, Asp, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 92
(D) OTHER INFORMATION: /note= "Xaa at position 92 is Glu or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 94
(C) OTHER INFORMATION: /note= "Xaa at position 94 is Arg, Ala, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 95
(D) OTHER INFORMATION: /note= "Xaa at position 95 is Arg, Thr, Glu, Leu, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 98
(D) OTHER INFORMATION: /note= "Xaa at position 98 is Thr, Val, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 100
(D) OTHER INFORMATION: /note= "Xaa at position 100 is Tyr or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 101
(D) OTHER INFORMATION: /note= "Xaa at position 101 is Leu or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 102

(D) OTHER INFORMATION: /note= "Xaa at position 102 is Lys, Thr, Val, Trp, Ser, Ala, His, Met, Phe, Tyr, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 103
(D) OTHER INFORMATION: /note= "Xaa at position 103 is Thr or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 106
(D) OTHER INFORMATION: /note= "Xaa at position 106 is Asn, Pro, Leu, His, Val, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 107
(D) OTHER INFORMATION: /note= "Xaa at position 107 is Ala, Ser, Ile, Asn, Pro, Asp, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 108
(D) OTHER INFORMATION: /note= "Xaa at position 108 is Gln, Ser, Met, Trp, Arg, Phe, Pro, His, Ile, Tyr, or Cys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 109
(D) OTHER INFORMATION: /note= "Xaa at position 109 is Ala, Met, Glu, His, Ser, Pro, Tyr, or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
Asn Cys Xaa Xaa Xaa Ile Xaa Glu Xaa Xaa Xaa Xaa Leu Lys Xaa Xaa
1               5                   10                  15

Xaa Xaa Xaa Xaa Xaa Asp Xaa Xaa Asn Leu Asn Xaa Glu Xaa Xaa Xaa
            20                  25                  30

Ile Leu Met Xaa Xaa Asn Leu Xaa Xaa Xaa Asn Leu Glu Xaa Phe Xaa
        35                  40                  45

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn Xaa Xaa Xaa Ile Glu Xaa Xaa Leu
    50                  55                  60

Xaa Xaa Leu Xaa Xaa Cys Xaa Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg
65                  70                  75                  80

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Asp Xaa Xaa Xaa Phe Xaa Xaa Lys
                85                  90                  95

Leu Xaa Phe Xaa Xaa Xaa Xaa Leu Glu Xaa Xaa Xaa Xaa Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Met- or Met-Ala- may or may not precede the amino acid in position 1"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 3
(D) OTHER INFORMATION: /note= "Xaa at position 3 is Ser, Gly, Asp, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 4
(D) OTHER INFORMATION: /note= "Xaa at position 4 is Asn, His, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 9
(D) OTHER INFORMATION: /note= "Xaa at position 9 is Ile, Ala, Leu, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 11
(D) OTHER INFORMATION: /note= "Xaa at position 11 is Thr, His, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 12
(D) OTHER INFORMATION: /note= "Xaa at position 12 is His or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 15
(D) OTHER INFORMATION: /note= "Xaa at position 15 is Gln or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 16
(D) OTHER INFORMATION: /note= "Xaa at position 16 is Pro or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 18
(D) OTHER INFORMATION: /note= "Xaa at position 18 is Leu, Arg, Asn, or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 20
(D) OTHER INFORMATION: /note= "Xaa at position 20 is Leu, Val, Ser, Ala, Arg, Gln, Glu, Ile, Phe, Thr, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 21
(D) OTHER INFORMATION: /note= "Xaa at position 21 is Leu, Ala, Asn, or Pro"

(ix) FEATURE:

(A) NAME/KEY: Modified-site
(B) LOCATION: 24
(D) OTHER INFORMATION: /note= "Xaa at position 24 is Asn or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 28
(D) OTHER INFORMATION: /note= "Xaa at position 28 is Gly, Asp, Ser, Ala, Asn, Ile, Leu, Met, Tyr, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 31
(D) OTHER INFORMATION: /note= "Xaa at position 31 is Gln, Val, Met, Leu, Ala, Asn, Glu, or Lys"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 32
(D) OTHER INFORMATION: /note= "Xaa at position 32 is Asp, Phe, Ser, Ala, Gln, Glu, His, Val, or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 36
(D) OTHER INFORMATION: /note= "Xaa at position 36 is Glu, Asn, Ser, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 37
(D) OTHER INFORMATION: /note= "Xaa at position 37 is Asn, Arg, Pro, Thr, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 41
(D) OTHER INFORMATION: /note= "Xaa at position 41 is Arg, Leu, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 42
(D) OTHER INFORMATION: /note= "Xaa at position 42 is Pro, Gly, Ser, Ala, Asn, Val, Leu, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 48
(D) OTHER INFORMATION: /note= "Xaa at position 48 is Asn, Pro, or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 50
(D) OTHER INFORMATION: /note= "Xaa at position 50 is Ala or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 51
(D) OTHER INFORMATION: /note= "Xaa at position 51 is Val or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

(B) LOCATION: 53
(D) OTHER INFORMATION: /note= "Xaa at position 53 is Ser or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 54
(D) OTHER INFORMATION: /note= "Xaa at position 54 is Leu or Phe"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 55
(D) OTHER INFORMATION: /note= "Xaa at position 55 is Gln, Ala, Glu, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 62
(D) OTHER INFORMATION: /note= "Xaa at position 62 is Ser, Val, Asn, Pro, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 63
(D) OTHER INFORMATION: /note= "Xaa at position 63 is Ile or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 65
(D) OTHER INFORMATION: /note= "Xaa at position 65 is Lys, Asn, Met, Arg, Ile, or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 66
(D) OTHER INFORMATION: /note= "Xaa at position 66 is Asn, Gly, Glu, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 68
(D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu, Gln, Trp, Arg, Asp, Asn, Glu, His, Met, Phe, Ser, Thr, Tyr, or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 73
(D) OTHER INFORMATION: /note= "Xaa at position 73 is Leu or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 74
(D) OTHER INFORMATION: /note= "Xaa at position 74 is Ala or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 77
(D) OTHER INFORMATION: /note= "Xaa at position 77 is Ala or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

```
      (B) LOCATION: 79
      (D) OTHER INFORMATION: /note= "Xaa at position 79 is Thr,
          Asp, or Ala"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 81
      (D) OTHER INFORMATION: /note= "Xaa at position 81 is His,
          Pro, Arg, Val, Gly, Asn, Ser, or Thr"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 84
      (D) OTHER INFORMATION: /note= "Xaa at position 84 is His,
          Ile, Asn, Leu, Ala, Thr, Arg, Gln, Glu, Lys, Met,
          Ser, Tyr, Val, or Leu"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 85
      (D) OTHER INFORMATION: /note= "Xaa at position 85 is Ile
          or Leu"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 86
      (D) OTHER INFORMATION: /note= "Xaa at position 86 is Lys
          or Arg"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 87
      (D) OTHER INFORMATION: /note= "Xaa at position 87 is Asp,
          Pro, Met, Lys, His, Pro, Asn, Ile, Leu, or Tyr"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 91
      (D) OTHER INFORMATION: /note= "Xaa at position 91 is Asn,
          Pro, Ser, Ile, or Asp"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 94
      (D) OTHER INFORMATION: /note="Xaa at position 94 is Arg,
          Ala, or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 95
      (D) OTHER INFORMATION: /note= "Xaa at position 95 is Arg,
          Thr, Glu, Leu, or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 98
      (D) OTHER INFORMATION: /note= "Xaa at position 98 is Thr
          or Gln"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 102
      (D) OTHER INFORMATION: /note= "Xaa at position 102 is Lys,
          Val, Trp, or Ile"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
```

(B) LOCATION: 103
(D) OTHER INFORMATION: /note= "Xaa at position 103 is Thr, Ala, His, Phe, Tyr, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 106
(D) OTHER INFORMATION: /note= "Xaa at position 106 is Asn, Pro, Leu, His, Val, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 107
(D) OTHER INFORMATION: /note= "Xaa at position 107 is Ala, Ser, Ile, Pro, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 108
(D) OTHER INFORMATION: /note= "Xaa at position 108 is Gln, Met, Trp, Phe, Pro, His, Ile, or Tyr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 109
(D) OTHER INFORMATION: /note= "Xaa at position 109 is Ala, Met, Glu, Ser, or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Asn Cys Xaa Xaa Met Ile Asp Glu Xaa Ile Xaa Xaa Leu Lys Xaa Xaa
1               5                   10                  15

Pro Xaa Pro Xaa Xaa Asp Phe Xaa Asn Leu Asn Xaa Glu Asp Xaa Xaa
            20                  25                  30

Ile Leu Met Xaa Xaa Asn Leu Arg Xaa Xaa Asn Leu Glu Ala Phe Xaa
        35                  40                  45

Arg Xaa Xaa Lys Xaa Xaa Xaa Asn Ala Ser Ala Ile Glu Xaa Xaa Leu
    50                  55                  60

Xaa Xaa Leu Xaa Pro Cys Leu Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg
65                  70                  75                  80

Xaa Pro Ile Xaa Xaa Xaa Xaa Gly Asp Trp Xaa Glu Phe Xaa Xaa Lys
                85                  90                  95

Leu Xaa Phe Tyr Leu Xaa Xaa Leu Glu Xaa Xaa Xaa Xaa Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 133 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Met- may or may not precede

the amino acid in position 1"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 18
(D) OTHER INFORMATION: /note= "Xaa at position 18 is Asn or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 19
(D) OTHER INFORMAITON: /note= "Xaa at position 19 is Met, Ala, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 20
(D) OTHER INFORMATION: /note= "Xaa at position 20 is Ile, Pro, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 23
(D) OTHER INFORMATION: /note= "Xaa at position 23 is Ile, Ala, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 25
(D) OTHER INFORMATION: /note= "Xaa at position 25 is Thr or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 29
(D) OTHER INFORMATION: /note= "Xaa at position 29 is Gln, Arg, Val, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 32
(D) OTHER INFORMATION: /note= "Xaa at position 32 is Leu, Ala, Asn, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 34
(D) OTHER INFORMATION: /note= "Xaa at position 34 is Leu or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 37
(D) OTHER INFORMATION: /note= "Xaa at position 37 is Phe, Pro, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION; 38
(D) OTHER INFORMATION: /note= "Xaa at position 38 is Asn or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 42
(D) OTHER INFORMATION: /note= "Xaa at position 42 is Gly, Ala, Ser, Asp, or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 45
(D) OTHER INFORMATION: /note= "Xaa at position 45 is Gln, Val, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 46
(D) OTHER INFORMATION: /note= "Xaa at position 46 is Asp or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 49
(D) OTHER INFORMATION: /note= "Xaa at position 49 is Met, Ile, Leu, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 50
(D) OTHER INFORMATION: /note= "Xaa at position 50 is Glu or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 51
(D) OTHER INFORMATION: /note= "Xaa at position 51 is Asn, Arg, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 55
(D) OTHER INFORMATION: /note= "Xaa at position 55 is Arg, Leu, or Thr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 56
(D) OTHER INFORMATION: /note= "Xaa at position 56 is Pro or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 59
(D) OTHER INFORMATION: /note= "Xaa at position 59 is Glu or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 60
(D) OTHER INFORMATION: /note= "Xaa at position 60 is Ala or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 62
(D) OTHER INFORMATION: /note= "Xaa at position 62 is Asn Val, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 63
(D) OTHER INFORMATION: /note= "Xaa at position 63 is Arg or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site

(B) LOCATION: 65
(D) OTHER INFORMATION: /note= "Xaa at position 65 is Val or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 67
(D) OTHER INFORMATION: /note= "Xaa at position 67 is Ser, Asn, His, or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 69
(D) OTHER INFORMATION: /note= "Xaa at position 69 is Gln or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 73
(D) OTHER INFORMATION: /note= "Xaa at position 73 is Ala or Gly"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 76
(D) OTHER INFORMATION: /note= "Xaa at position 76 is Ser, Ala, or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 79
(D) OTHER INFORMATION: /note= "Xaa at position 79 is Lys, Arg, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 82
(D) OTHER INFORMATION: /note= "Xaa at position 82 is Leu, Glu, Val, or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 85
(D) OTHER INFORMATION: /note= "Xaa at position 85 is Leu or Val"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 87
(D) OTHER INFORMATION: /note= "Xaa at position 87 is Leu, Ser, or Tyr"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 88
(D) OTHER INFORMATION: /note= "Xaa at position 88 is Ala or Trp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 91
(D) OTHER INFORMATION: /note= "Xaa at position 91 is Ala or Pro"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 93
(D) OTHER INFORMATION: /note= "Xaa at position 93 is Pro

```
            or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 95
      (D) OTHER INFORMATION: /note= "Xaa at position 95 is His
            or Thr"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 98
      (D) OTHER INFORMATION: /note= "Xaa at position 98 is His,
            Ile, or Thr"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 100
      (D) OTHER INFORMATION: /note= "Xaa at position 100 is Lys
            or Arg"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 101
      (D) OTHER INFORMATION: /note= "Xaa at position 101 is Asp,
            Ala, or Met"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 105
      (D) OTHER INFORMATION: /note= "Xaa at position 105 is Asn
            or Glu"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 109
      (D) OTHER INFORMATION: /note= "Xaa at position 109 is Arg,
            Glu, or Leu"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 112
      (D) OTHER INFORMATION: /note= "Xaa at position 112 is Thr
            or Gln"
(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 116
      (D) OTHER INFORMATION: /note= "Xaa at position 116 is Lys,
            Val, Trp, or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 117
      (D) OTHER INFORMATION: /note= "Xaa at position 117 is Thr
            or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 120
      (D) OTHER INFORMATION: /note= "Xaa at position 120 is Asn,
            Gln, or His"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 123
      (D) OTHER INFORMATION: /note= "Xaa at position 123 is Ala
            or Glu"
```

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn Cys
1               5                  10                  15

Ser Xaa Xaa Xaa Asp Glu Xaa Ile Xaa His Leu Lys Xaa Pro Pro Xaa
            20                  25                  30

Pro Xaa Leu Asp Xaa Xaa Asn Leu Asn Xaa Glu Asp Xaa Xaa Ile Leu
        35                  40                  45

Xaa Xaa Xaa Asn Leu Arg Xaa Xaa Asn Leu Xaa Xaa Phe Xaa Xaa Ala
    50                  55                  60

Xaa Lys Xaa Leu Xaa Asn Ala Ser Xaa Ile Glu Xaa Ile Leu Xaa Asn
65                  70                  75                  80

Leu Xaa Pro Cys Xaa Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg Xaa Pro
                85                  90                  95

Ile Xaa Ile Xaa Xaa Gly Asp Trp Xaa Glu Phe Arg Xaa Lys Leu Xaa
            100                 105                 110

Phe Tyr Leu Xaa Xaa Leu Glu Xaa Ala Gln Xaa Gln Gln Thr Thr Leu
        115                 120                 125

Ser Leu Ala Ile Phe
    130
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 1
(D) OTHER INFORMATION: /note= "Met- or Met-Ala may or may not precede the amino acid in position 1"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 4
(D) OTHER INFORMATION: /note= "Xaa at position 4 is Asn or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 5
(D) OTHER INFORMATION: /note= "Xaa at position 5 is Met, Ala, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 6
(D) OTHER INFORMATION: /note= "Xaa at position 6 is Ile, Pro, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 9

(D) OTHER INFORMATION: /note= "Xaa at position 9 is Ile, Ala, or Leu"

(ix) FEATURE:
(A) NAM/KEY: Modified-site
(B) LOCATION: 11
(D) OTHER INFORMATION: /note= "Xaa at position 11 is Thr or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 15
(D) OTHER INFORMATION: /note= "Xaa at position 15 is Gln, Arg, Val, or Ile"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 18
(D) OTHER INFORMATION: /note= "Xaa at position 18 is Leu, Ala, Asn, or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 20
(D) OTHER INFORMATION: /note= "Xaa at position 20 is Leu or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 23
(D) OTHER INFORMATION: /note= "Xaa at position 23 is Phe, Pro, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 24
(D) OTHER INFORMATION: /note= "Xaa at position 24 is Asn or Ala"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 28
(D) OTHER INFORMATION: /note= "Xaa at position 28 is Gly, Ala, Ser, Asp, or Asn"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 31
(D) OTHER INFORMATION: /note= "Xaa at position 31 is Gln, Val, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 32
(D) OTHER INFORMATION: /note= "Xaa at position 32 is Asp or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 35
(D) OTHER INFORMATION: /note= "Xaa at position 35 is Met, Ile, or Asp"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION 36
(D) OTHER INFORMATION: /note= "Xaa at position 36 is Glu or Asp"

```
(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 37
      (D) OTHER INFORMATION: /note= "Xaa at position 37 is Asn,
          Arg, or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 41
      (D) OTHER INFORMATION: /note= "Xaa at position 41 is Arg,
          Leu, or Thr"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION 42
      (D) OTHER INFORMATION: /note= "Xaa at position 42 is Pro
          or Ser"
(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 45
      (D) OTHER INFORMATION: /note= "Xaa at position 45 is Glu
          or Leu"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 46
      (D) OTHER INFORMATION: /note= "Xaa at position 46 is Ala
          or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 48
      (D) OTHER INFORMATION: /note= "Xaa at position 48 is Asn,
          Val, or Pro"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 49
      (D) OTHER INFORMATION: /note= "Xaa at position 49 is Arg
          or His"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 51
      (D) OTHER INFORMATION: /note= "Xaa at position 51 is Val
          or Ser"
(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 53
      (D) OTHER INFORMATION: /note= "Xaa at position 53 is Ser,
          Asn, His, or Gln"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 55
      (D) OTHER INFORMATION: /note= "Xaa at position 55 is Gln
          or Glu"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 59
      (D) OTHER INFORMATION: /note= "Xaa at position 59 is Ala
          or Gly"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
```

```
      (B) LOCATION: 62
      (D) OTHER INFORMATION: /note= "Xaa at position 62 is Ser,
          Ala, or Pro"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 65
      (D) OTHER INFORMATION: /note= "Xaa at position 65 is Lys,
          Arg, or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 67
      (D) OTHER INFORMATION: /note= "Xaa at position 67 is Leu,
          Glu, or Val"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 68
      (D) OTHER INFORMATION: /note= "Xaa at position 68 is Leu,
          Glu, Val, or Trp"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION 71
      (D) OTHER INFORMATION: /note= "Xaa at position 71 is Leu
          or Val"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 73
      (D) OTHER INFORMATION: /note= "Xaa at position 73 is Leu,
          Ser, or Tyr"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 74
      (D) OTHER INFORMATION: /note= "Xaa at position 74 is Ala
          or Trp"

(ix) FEATURE:
     (A) NAME/KEY: Modified-site
     (B) LOCATION: 77
     (D) OTHER INFORMATION: /note= "Xaa at position 77 is Ala
         or Pro"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 79
      (D) OTHER INFORMATION: /note= "Xaa at position 79 is Pro
          or Ser"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 81
      (D) OTHER INFORMATION: /note= "Xaa at position 81 is His
          or Thr"
(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 84
      (D) OTHER INFORMATION: /note= "Xaa at position 84 is His,
          Ile, or Thr"

(ix) FEATURE:
      (A) NAME/KEY: Modified-site
      (B) LOCATION: 86
      (D) OTHER INFORMATION: /note= "Xaa at position 86 is Lys
```

or Arg"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 87
(D) OTHER INFORMATION: /note= "Xaa at position 87 is Asp, Ala, or Met"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 91
(D) OTHER INFORMATION: /note= "Xaa at position 91 is Asn or Glu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 95
(D) OTHER INFORMATION: /note= "Xaa at position 95 is Arg, Glu, or Leu"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 98
(D) OTHER INFORMATION: /note= "Xaa at position 98 is Thr or Gln"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 102
(D) OTHER INFORMATION: /note= "Xaa at position 102 is Lys, Val, Trp, or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 103
(D) OTHER INFORMATION: /note= "Xaa at position 103 is Thr or Ser"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 106
(D) OTHER INFORMATION: /note= "Xaa at position 106 is Asn, Gln, or His"

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 109
(D) OTHER INFORMATION: /note= "Xaa at position 109 is Ala or Glu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
Asn Cys Ser Xaa Xaa Xaa Asp Glu Xaa Ile Xaa His Leu Lys Xaa Pro
1               5                   10                  15

Pro Xaa Pro Xaa Leu Asp Xaa Xaa Asn Leu Asn Xaa Glu Asp Xaa Xaa
            20                  25                  30

Ile Leu Xaa Xaa Xaa Asn Leu Arg Xaa Xaa Asn Leu Xaa Xaa Phe Xaa
        35                  40                  45

Xaa Ala Xaa Lys Xaa Leu Xaa Asn Ala Ser Xaa Ile Glu Xaa Ile Leu
    50                  55                  60

Xaa Asn Xaa Xaa Pro Cys Xaa Pro Xaa Xaa Thr Ala Xaa Pro Xaa Arg
65                  70                  75                  80
```

Xaa Pro Ile Xaa Ile Xaa Xaa Gly Asp Trp Xaa Glu Phe Arg Xaa Lys
85 90 95

Leu Xaa Phe Tyr Leu Xaa Xaa Leu Glu Xaa Ala Gln Xaa Gln Gln
100 105 110

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro
1 5 10 15

Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp Val Asp
20 25 30

Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
35 40 45

Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu
50 55 60

Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
65 70 75 80

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
85 90 95

Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
100 105 110

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro
1 5 10 15

Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp
20 25 30

Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
35 40 45

Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu
50 55 60

Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
65 70 75 80

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
85 90 95

Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
100 105 110

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Val Pro
1 5 10 15

Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp Met Asp
20 25 30

Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
35 40 45

Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu
50 55 60

Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
65 70 75 80

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
85 90 95

Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
100 105 110

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
1 5 10 15

Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
20 25 30

Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala Phe Val
35 40 45

Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu
50 55 60

Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg

65 70 75 80

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
85 90 95

Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
100 105 110

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
1 5 10 15

Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
20 25 30

Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val
35 40 45

Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu
50 55 60

Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
65 70 75 80

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
85 90 95

Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
100 105 110

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
1 5 10 15

Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
20 25 30

Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val
35 40 45

Arg Ala Val Lys His Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu
50 55 60

```
Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
65                  70                  75                  80

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
                85                  90                  95

Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
1               5                   10                  15

Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
            20                  25                  30

Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
        35                  40                  45

Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu
    50                  55                  60

Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg
65                  70                  75                  80

His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Arg Lys
                85                  90                  95

Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
1               5                   10                  15

Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
            20                  25                  30

Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
        35                  40                  45

Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu
    50                  55                  60
```

```
Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg
65                  70                  75                  80

His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Arg Lys
                85                  90                  95

Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

```
Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
1               5                   10                  15

Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
            20                  25                  30

Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
        35                  40                  45

Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu
    50                  55                  60

Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
65                  70                  75                  80

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Glu Lys
                85                  90                  95

Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
1               5                   10                  15

Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
            20                  25                  30

Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
        35                  40                  45

Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu
```

```
     50                  55                  60

Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
65                  70                  75                  80

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Glu Lys
                85                  90                  95

Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
1               5                   10                  15

Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
            20                  25                  30

Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
        35                  40                  45

Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu
    50                  55                  60

Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg
65                  70                  75                  80

His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys
                85                  90                  95

Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
1               5                   10                  15

Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
            20                  25                  30

Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
        35                  40                  45
```

```
Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu
    50                  55                  60

Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg
65                  70                  75                  80

His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys
                85                  90                  95

Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro
1               5                   10                  15

Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp
            20                  25                  30

Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn
        35                  40                  45

Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala Ile Leu
    50                  55                  60

Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg
65                  70                  75                  80

His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys
                85                  90                  95

Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

```
Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro
1               5                   10                  15

Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp Val Asp
            20                  25                  30

Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val
        35                  40                  45
```

```
Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu
    50                  55                  60

Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
65                  70                  75                  80

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
                85                  90                  95

Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro
1               5                   10                  15

Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp
            20                  25                  30

Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val
        35                  40                  45

Arg Ala Val Lys His Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu
    50                  55                  60

Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
65                  70                  75                  80

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
                85                  90                  95

Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Val Pro
1               5                   10                  15

Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp Met Asp
            20                  25                  30

Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala Phe Val
```

```
         35                  40                  45

Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser Ile Leu
    50                  55                  60

Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg
65                  70                  75                  80

His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys
                85                  90                  95

Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys
1               5                   10                  15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp
            20                  25                  30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
        35                  40                  45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```
Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys
1               5                   10                  15
```

```
Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp
            20                  25                  30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
        35                  40                  45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

```
Met Ala Asn Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys
1               5                   10                  15

Gln Pro Pro Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp
            20                  25                  30

Gln Asp Ile Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala
        35                  40                  45

Phe Asn Arg Ala Val Lys Ser Leu Gln Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1               5                  10                  15

Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp
            20                  25                  30

Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
        35                  40                  45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser
    50                  55                  60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
65                  70                  75                  80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
                85                  90                  95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1               5                  10                  15

Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp
            20                  25                  30

Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
        35                  40                  45

Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Ala Ile Glu Ser
    50                  55                  60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
65                  70                  75                  80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
                85                  90                  95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1               5                  10                  15

Val Pro Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp
            20                  25                  30

Met Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala
        35                  40                  45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Ala Ile Glu Ser
    50                  55                  60

Ile Leu Lys Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro
65                  70                  75                  80

Thr Arg His Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg
                85                  90                  95

Arg Lys Leu Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1               5                  10                  15

Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp
            20                  25                  30

Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
        35                  40                  45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
```

100 105 110

Gln

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1 5 10 15

Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp
20 25 30

Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
35 40 45

Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala
50 55 60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65 70 75 80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
85 90 95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
100 105 110

Gln

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1 5 10 15

Val Pro Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp
20 25 30

Met Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala
35 40 45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
50 55 60

```
Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1               5                   10                  15

Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp
            20                  25                  30

Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
        35                  40                  45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1               5                   10                  15

Val Pro Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp
            20                  25                  30
```

Met Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala
35 40 45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
50 55 60

Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65 70 75 80

Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
85 90 95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
100 105 110

Gln

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1 5 10 15

Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp
20 25 30

Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
35 40 45

Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala
50 55 60

Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65 70 75 80

Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
85 90 95

Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln
100 105 110

Gln

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1               5                   10                  15

Val Pro Pro Ala Pro Leu Leu Asp Ser Asn Asn Leu Asn Ser Glu Asp
            20                  25                  30

Met Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Leu Ala
        35                  40                  45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1               5                   10                  15

Arg Pro Pro Asn Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp
            20                  25                  30

Met Asp Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
        35                  40                  45

Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1               5                   10                  15

Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp
            20                  25                  30

Val Asp Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
        35                  40                  45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Val Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Thr Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Ser Leu Glu His Ala Gln Glu Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1               5                   10                  15

Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp
            20                  25                  30

Val Asp Ile Leu Met Asp Arg Asn Leu Arg Leu Ser Asn Leu Glu Ser
        35                  40                  45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
            100                 105                 110
```

Gln

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ala Ile His His Leu Lys
1               5                   10                  15

Arg Pro Pro Ala Pro Ser Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp
            20                  25                  30

Met Ser Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
        35                  40                  45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1               5                   10                  15

Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp
            20                  25                  30

Met Ser Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
        35                  40                  45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80
```

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
85 90 95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
100 105 110

Gln

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1 5 10 15

Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp
20 25 30

Val Asp Ile Leu Met Asp Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
35 40 45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
50 55 60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65 70 75 80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
85 90 95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
100 105 110

Gln

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1 5 10 15

Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp
20 25 30

Val Ser Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser

```
         35                  40                  45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys
1               5                   10                  15

Arg Pro Pro Ala Pro Leu Leu Asp Pro Asn Asn Leu Asn Asp Glu Asp
            20                  25                  30

Met Ser Ile Leu Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser
        35                  40                  45

Phe Val Arg Ala Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 125 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

```
Met Ala Tyr Pro Glu Thr Asp Tyr Lys Asp Asp Asp Asp Lys Asn Cys
1               5                  10                  15

Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Ala
            20                  25                  30

Pro Leu Leu Asp Pro Asn Asn Leu Asn Ala Glu Asp Val Asp Ile Leu
        35                  40                  45

Met Glu Arg Asn Leu Arg Leu Pro Asn Leu Glu Ser Phe Val Arg Ala
    50                  55                  60

Val Lys Asn Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn
65                  70                  75                  80

Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
                85                  90                  95

Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr
            100                 105                 110

Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln
        115                 120                 125
```

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 125 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

```
Met Ala Tyr Pro Glu Thr Asp Tyr Lys Asp Asp Asp Asp Lys Asn Cys
1               5                  10                  15

Ser Ile Met Ile Asp Glu Ile Ile His His Leu Lys Arg Pro Pro Asn
            20                  25                  30

Pro Leu Leu Asp Pro Asn Asn Leu Asn Ser Glu Asp Met Asp Ile Leu
        35                  40                  45

Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala Phe Val Arg Ala
    50                  55                  60

Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala Ile Leu Arg Asn
65                  70                  75                  80

Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro Ser Arg His Pro
                85                  90                  95

Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg Glu Lys Leu Thr
            100                 105                 110

Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln Gln
        115                 120                 125
```

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

```
Met Ala Asn Cys Ser Ile Met Ile Asp Glu Leu Ile His His Leu Lys
1               5                   10                  15

Ile Pro Pro Asn Pro Ser Leu Asp Ser Ala Asn Leu Asn Ser Glu Asp
            20                  25                  30

Val Ser Ile Leu Met Glu Arg Asn Leu Arg Thr Pro Asn Leu Leu Ala
        35                  40                  45

Phe Val Arg Ala Val Lys His Leu Glu Asn Ala Ser Gly Ile Glu Ala
    50                  55                  60

Ile Leu Arg Asn Leu Gln Pro Cys Leu Pro Ser Ala Thr Ala Ala Pro
65                  70                  75                  80

Ser Arg His Pro Ile Ile Ile Lys Ala Gly Asp Trp Gln Glu Phe Arg
                85                  90                  95

Glu Lys Leu Thr Phe Tyr Leu Val Thr Leu Glu Gln Ala Gln Glu Gln
            100                 105                 110

Gln
```

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 134 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

```
Met Ala Pro Met Thr Gln Thr Thr Ser Leu Lys Thr Ser Trp Val Asn
1               5                   10                  15

Cys Ser Asn Met Ile Asp Glu Ile Ile Thr His Leu Lys Gln Pro Pro
            20                  25                  30

Leu Pro Leu Leu Asp Phe Asn Asn Leu Asn Gly Glu Asp Gln Asp Ile
        35                  40                  45

Leu Met Glu Asn Asn Leu Arg Arg Pro Asn Leu Glu Ala Phe Asn Arg
    50                  55                  60

Ala Val Lys Ser Leu Gln Asn Ala Ser Ala Ile Glu Ser Ile Leu Lys
65                  70                  75                  80

Asn Leu Leu Pro Cys Leu Pro Leu Ala Thr Ala Ala Pro Thr Arg His
                85                  90                  95

Pro Ile His Ile Lys Asp Gly Asp Trp Asn Glu Phe Arg Arg Lys Leu
            100                 105                 110

Thr Phe Tyr Leu Lys Thr Leu Glu Asn Ala Gln Ala Gln Gln Thr Thr
        115                 120                 125
```

Leu Ser Leu Ala Ile Phe
130

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "synthetic DNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CATGGCAAGA TCTCCGGCCA GAATGGAGCT GACTGA 36

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "synthetic DNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

AATAGCTGAA TTCTTACCCT TCCTGAGACA GATT 34

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "synthetic DNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ACGTCCATGG CNTCNCCNGC NCCNCCTGCT TGTGACCTCC GAGTC 45

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "synthetic DNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TGACAAGCTT ACCTGACGCA GAGGGTGGAC CCT 33

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 465 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

ATGGCGTCTC CGGCGCCGCC TGCTTGTGAC CTCCGAGTCC TCAGTAAACT GCTTCGTGAC 60

TCCCATGTCC TTCACAGCAG ACTGAGCCAG TGCCCAGAGG TTCACCCTTT GCCTACACCT 120

GTCCTGCTGC CTGCTGTGGA CTTTAGCTTG GGAGAATGGA AAACCCAGAT GGAGGAGACC 180

AAGGCACAGG ACATTCTGGG AGCAGTGACC CTTCTGCTGG AGGGAGTGAT GGCAGCACGG 240

GGACAACTGG GACCCACTTG CCTCTCATCC CTCCTGGGGC AGCTTTCTGG ACAGGTCCGT 300

CTCCTCCTTG GGGCCCTGCA GAGCCTCCTT GGAACCCAGC TTCCTCCACA GGGCAGGACC 360

ACAGCTCACA AGGATCCCAA TGCCATCTTC CTGAGCTTCC AACACCTGCT CCGAGGAAAG 420

GTGCGTTTCC TGATGCTTGT AGGAGGGTCC ACCCTCTGCG TCAGG 465

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 353 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Met Glu Leu Thr Glu Leu Leu Leu Val Val Met Leu Leu Leu Thr Ala
1 5 10 15

Arg Leu Thr Leu Ser Ser Pro Ala Pro Pro Ala Cys Asp Leu Arg Val
20 25 30

Leu Ser Lys Leu Leu Arg Asp Ser His Val Leu His Ser Arg Leu Ser
35 40 45

```
Gln Cys Pro Glu Val His Pro Leu Pro Thr Pro Val Leu Leu Pro Ala
     50                  55                  60

Val Asp Phe Ser Leu Gly Glu Trp Lys Thr Gln Met Glu Glu Thr Lys
65                  70                  75                  80

Ala Gln Asp Ile Leu Gly Ala Val Thr Leu Leu Leu Glu Gly Val Met
                85                  90                  95

Ala Ala Arg Gly Gln Leu Gly Pro Thr Cys Leu Ser Ser Leu Leu Gly
            100                 105                 110

Gln Leu Ser Gly Gln Val Arg Leu Leu Leu Gly Ala Leu Gln Ser Leu
        115                 120                 125

Leu Gly Thr Gln Leu Pro Pro Gln Gly Arg Thr Thr Ala His Lys Asp
    130                 135                 140

Pro Asn Ala Ile Phe Leu Ser Phe Gln His Leu Leu Arg Gly Lys Val
145                 150                 155                 160

Arg Phe Leu Met Leu Val Gly Gly Ser Thr Leu Cys Val Arg Arg Ala
                165                 170                 175

Pro Pro Thr Thr Ala Val Pro Ser Arg Thr Ser Leu Val Leu Thr Leu
            180                 185                 190

Asn Glu Leu Pro Asn Arg Thr Ser Gly Leu Leu Glu Thr Asn Phe Thr
        195                 200                 205

Ala Ser Ala Arg Thr Thr Gly Ser Gly Leu Leu Lys Trp Gln Gln Gly
    210                 215                 220

Phe Arg Ala Lys Ile Pro Gly Leu Leu Asn Gln Thr Ser Arg Ser Leu
225                 230                 235                 240

Asp Gln Ile Pro Gly Tyr Leu Asn Arg Ile His Glu Leu Leu Asn Gly
                245                 250                 255

Thr Arg Gly Leu Phe Pro Gly Pro Ser Arg Arg Thr Leu Gly Ala Pro
            260                 265                 270

Asp Ile Ser Ser Gly Thr Ser Asp Thr Gly Ser Leu Pro Pro Asn Leu
        275                 280                 285

Gln Pro Gly Tyr Ser Pro Ser Pro Thr His Pro Pro Thr Gly Gln Tyr
    290                 295                 300

Thr Leu Phe Pro Leu Pro Pro Thr Leu Pro Thr Pro Val Val Gln Leu
305                 310                 315                 320

His Pro Leu Leu Pro Asp Pro Ser Ala Pro Thr Pro Thr Pro Thr Ser
                325                 330                 335

Pro Leu Leu Asn Thr Ser Tyr Thr His Ser Gln Asn Leu Ser Gln Glu
            340                 345                 350

Gly
```

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

```
Met Glu Leu Thr Glu Leu Leu Leu Val Val Met Leu Leu Leu Thr Ala
1               5                  10                  15

Arg Leu Thr Leu Ser Ser Pro Ala Pro Pro Ala Cys Asp Leu Arg Val
            20                  25                  30

Leu Ser Lys Leu Leu Arg Asp Ser His Val Leu His Ser Arg Leu Ser
        35                  40                  45

Gln Cys Pro Glu Val His Pro Leu Pro Thr Pro Val Leu Leu Pro Ala
    50                  55                  60

Val Asp Phe Ser Leu Gly Glu Trp Lys Thr Gln Met Glu Glu Thr Lys
65                  70                  75                  80

Ala Gln Asp Ile Leu Gly Ala Val Thr Leu Leu Leu Glu Gly Val Met
                85                  90                  95

Ala Ala Arg Gly Gln Leu Gly Pro Thr Cys Leu Ser Ser Leu Leu Gly
            100                 105                 110

Gln Leu Ser Gly Gln Val Arg Leu Leu Leu Gly Ala Leu Gln Ser Leu
        115                 120                 125

Leu Gly Thr Gln Leu Pro Pro Gln Gly Arg Thr Thr Ala His Lys Asp
    130                 135                 140

Pro Asn Ala Ile Phe Leu Ser Phe Gln His Leu Leu Arg Gly Lys Val
145                 150                 155                 160

Arg Phe Leu Met Leu Val Gly Gly Ser Thr Leu Cys Val Arg
                165                 170
```

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1059 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

```
ATGGAGCTGA CTGAATTGCT CCTCGTGGTC ATGCTTCTCC TAACTGCAAG GCTAACGCTG      60

TCCAGCCCGG CTCCTCCTGC TTGTGACCTC CGAGTCCTCA GTAAACTGCT TCGTGACTCC     120

CATGTCCTTC ACAGCAGACT GAGCCAGTGC CCAGAGGTTC ACCCTTTGCC TACACCTGTC     180

CTGCTGCCTG CTGTGGACTT TAGCTTGGGA GAATGGAAAA CCCAGATGGA GGAGACCAAG     240

GCACAGGACA TTCTGGGAGC AGTGACCCTT CTGCTGGAGG GAGTGATGGC AGCACGGGGA     300
```

CAACTGGGAC CCACTTGCCT CTCATCCCTC CTGGGGCAGC TTTCTGGACA GGTCCGTCTC 360

CTCCTTGGGG CCCTGCAGAG CCTCCTTGGA ACCCAGCTTC CTCCACAGGG CAGGACCACA 420

GCTCACAAGG ATCCCAATGC CATCTTCCTG AGCTTCCAAC ACCTGCTCCG AGGAAAGGTG 480

CGTTTCCTGA TGCTTGTAGG AGGGTCCACC CTCTGCGTCA GGCGGGCCCC ACCCACCACA 540

GCTGTCCCCA GCAGAACCTC TCTAGTCCTC ACACTGAACG AGCTCCCAAA CAGGACTTCT 600

GGATTGTTGG AGACAAACTT CACTGCCTCA GCCAGAACTA CTGGCTCTGG GCTTCTGAAG 660

TGGCAGCAGG GATTCAGAGC CAAGATTCCT GGTCTGCTGA ACCAAACCTC CAGGTCCCTG 720

GACCAAATCC CCGGATACCT GAACAGGATA CACGAACTCT TGAATGGAAC TCGTGGACTC 780

TTTCCTGGAC CCTCACGCAG GACCCTAGGA GCCCCGGACA TTTCCTCAGG AACATCAGAC 840

ACAGGCTCCC TGCCACCCAA CCTCCAGCCT GGATATTCTC CTTCCCCAAC CCATCCTCCT 900

ACTGGACAGT ATACGCTCTT CCCTCTTCCA CCCACCTTGC CCACCCCTGT GGTCCAGCTC 960

CACCCCCTGC TTCCTGACCC TTCTGCTCCA ACGCCCACCC CTACCAGCCC TCTTCTAAAC 1020

ACATCCTACA CCCACTCCCA GAATCTGTCT CAGGAAGGG 1059

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 408 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA other nucleic acid
(A) DESCRIPTION: /desc = "synthetic DNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

ATGGCTCCAA TGACTCAGAC TACTTCTCTT AAGACTTCTT GGGTTAACTG CTCTAACATG 60

ATCGATGAAA TTATAACACA CTTAAAGCAG CCACCTTTGC CTTTGCTGGA CTTCAACAAC 120

CTCAATGGGG AAGACCAAGA CATTCTGATG GAAAATAACC TTCGAAGGCC AAACCTGGAG 180

GCATTCAACA GGGCTGTCAA GAGTTTACAG AATGCATCAG CAATTGAGAG CATTCTTAAA 240

AATCTCCTGC CATGTCTGCC CCTGGCCACG GCCGCACCCA CGCGACATCC AATCCATATC 300

AAGGACGGTG ACTGGAATGA ATTCCGTCGT AAACTGACCT TCTATCTGAA AACCTTGGAG 360

AACGCGCAGG CTCAACAGAC CACTCTGTCG CTAGCGATCT TTTAATAA 408